Genes, Environment, and Eating Disorders: What the Clinician Needs to Know

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Disclosures

- Shire Pharmaceuticals (grant recipient; advisory board)
- Idorsia (consultant)
- Pearson (author)
Talk Map

- Genetics of eating disorders landscape
- Understanding current results
- Clinicians’ responsibility
- Now!
# Topography of Feeding and Eating Disorders (DSM-5)

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anorexia Nervosa</strong></td>
<td>- Low Weight</td>
</tr>
<tr>
<td></td>
<td>- Intense fear of weight gain</td>
</tr>
<tr>
<td></td>
<td>- Inability to recognize seriousness of low weight</td>
</tr>
<tr>
<td><strong>Bulimia Nervosa</strong></td>
<td>- Binge eating</td>
</tr>
<tr>
<td></td>
<td>- Regular compensatory behaviors</td>
</tr>
<tr>
<td></td>
<td>- Normal, overweight, obese</td>
</tr>
<tr>
<td><strong>Binge-Eating Disorder</strong></td>
<td>- Binge eating</td>
</tr>
<tr>
<td></td>
<td>- No regular compensatory behaviors</td>
</tr>
<tr>
<td></td>
<td>- Distress</td>
</tr>
<tr>
<td></td>
<td>- Often overweight/obese</td>
</tr>
<tr>
<td><strong>Avoidant and Restrictive Food Intake Disorder (ARFID)</strong></td>
<td>- Feeding disturbance, refusal, fear</td>
</tr>
<tr>
<td></td>
<td>- Nutritional deficiencies</td>
</tr>
<tr>
<td></td>
<td>- Weight loss or failure to gain</td>
</tr>
</tbody>
</table>
### Eating Disorders

<table>
<thead>
<tr>
<th>Eating disorders (EDs)</th>
<th>Anorexia nervosa (AN)</th>
<th>Bulimia nervosa (BN)</th>
<th>Binge-eating disorder (BED)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epidemiology</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Lifetime prevalence</td>
<td>&lt;1-4%</td>
<td>&lt;1-2%</td>
<td>1-4%</td>
</tr>
<tr>
<td>- Mortality (SMR)</td>
<td>~5.4</td>
<td>~1.5</td>
<td>~1.5</td>
</tr>
<tr>
<td><strong>Heritability</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(twin-based)</td>
<td>~60%</td>
<td>~60%</td>
<td>~45%</td>
</tr>
<tr>
<td><strong>GWAS</strong></td>
<td>8 independent loci</td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>

### References
- Keski-Rahkonen & Mustelin, 2016
- Fichter et al., 2016
- Yilmaz, Hardaway, Bulik, 2015
- Watson et al., 2019

Slide courtesy of Jet Termorshuizen
Why study the genetics of eating disorders?
Eating disorders genetics informs other phenotypes

Knowledge about eating disorders informs our understanding of many related phenotypes.
GWAS basics

Variant #1 (C/T)
Less common: C
Cases 62%
Controls 38%

Variant #2 (A/G)
Less common: G
Cases 49%
Controls 51%

Variant #3
Variant #4

Current or past AN
Cases
No history of eating disorders
Controls

ATTGGGC\textcolor{red}{C}GAGTGTCTAACCCG
ATTGGG\textcolor{red}{T}GAGTGTCTGGCCCG
How to read a Manhattan plot

Significance level

Chromosome

$5 \times 10^{-8}$
Eating Disorders Working Group of the Psychiatric Genomics Consortium (PGC-ED)
Composition of PGC-ED Freeze 2

33 datasets with 16,992 cases and 55,525 controls from 17 countries
GWAS Results

SNP-$h^2$ 11–17% (se = 1%)

IBD, ulcerative colitis, Crohn’s, macrophage functions, blood protein levels, obesity-related traits, HDL, Parkinson’s

Esophageal adenocarcinoma, Barrett’s esophagus, intellectual disability

temozolomide response

Age at menarche, obesity, body fat

Autoimmune
Metabolic
Neuropsychiatric
Sex hormones

Sjögren’s Syndrome
BMI

Hunna Watson, PhD
Nature Genetics
PMID: 31308545
There’s Valuable Information Below the Red Line!
Genetic Correlations

- Estimates genetic correlations from published summary statistics
- Do not need to measure all of the traits on the same people
- Between diseases, “genetic analogue of comorbidity”
- Not phenotypic correlations…genetic correlations!

Brendan Bulik-Sullivan
Genetic Correlations with Anorexia

Psychiatric disorder/trait
Major depressive disorder (PGC)
Obsessive-compulsive disorder (PGC)
Schizophrenia (PGC)
Depressive symptoms
Anxiety (UKB)
Neuroticism (UKB)
Years of education
College completion

Personality trait
Attainment of a college or a university degree
Physical activity (objectively-measured)
HOMA-IR: Insulin resistance (age- & sex-adjusted)
Fasting insulin (age- & sex-adjusted)
Leptin (not BMI-adjusted)
Fasting insulin (BMI-adjusted)
Type 2 diabetes
HDL cholesterol

Educational attainment
Body fat percentage (UKB)
Fat mass (UKB)
Body mass index (UKB)
Waist circumference
Overweight (BMI 25-30)
Obesity class 1 (BMI 30-35)

Physical activity
Waist-to-hip ratio
Hip circumference

Metabolic trait
Extreme body mass index
Obesity class 2 (BMI 35-40)

Anthropometric trait
Waist circumference (BMI-adjusted)
Fat-free mass

Genetic correlation $r_g$
Genetic Correlations Between Anorexia and Psychiatric, Educational, and Physical Activity

Obsessive-compulsive disorder (PGC)
Major depressive disorder (PGC)
Schizophrenia (PGC)
Anxiety (UKB)
Depressive symptoms
Neuroticism (UKB)
Years of education
College completion
Attainment of a college or a university degree
Physical activity (objectively-measured)
Genetic Correlations Between Anorexia and Metabolic Factors

- HOMA-IR: Insulin resistance (age- & sex-adjusted)
- Fasting insulin (age- & sex-adjusted)
- Leptin (not BMI-adjusted)
- Fasting insulin (BMI-adjusted)
- Type 2 diabetes
- HDL cholesterol
Genetic Correlations Between Anorexia and Anthropometric / Body Measurement Factors

- Body fat percentage (UKB)
- Fat mass (UKB)
- Body mass index (UKB)
- Waist circumference
- Overweight (BMI 25-30)
- Obesity class 1 (BMI 30-35)
- Waist-to-hip ratio
- Hip circumference
- Extreme body mass index
- Obesity class 2 (BMI 35-40)
- Waist circumference (BMI-adjusted)
- Fat-free mass

Genetic correlation $r_g$

Negative (-)

Positive (+)
Reconceptualizing Anorexia Nervosa as Metabo-Psychiatric

- Perplexing ability to reach and maintain low BMI
- Frequent return to a “negative settling point”
- Negative genetic correlations with BMI and other “unfavorable” metabolic parameters
- Positive genetic correlations with HDL
- Prefer a state of negative energy balance (expending more energy than consuming)
Implications and Next Steps

- Greater attention to metabolic factors may improve outcome (only 30% recover)
- Explanation for why adequate renourishment is essential to prevent relapse?
- Need to understand metabolic mechanisms!
- What about the other eating disorders?

PMID: 28644530
What About the Other Eating Disorders?

One size does not fit all. Genomics differentiates among anorexia nervosa, bulimia nervosa, and binge-eating disorder

Christopher Hübel MD, PhD1,2,3,4 | Mohamed Abdulkadir MSc5,6 |
Moritz Herle PhD7 | Ruth J. F. Loos PhD8 | Gerome Breen PhD1,2 |
Cynthia M. Bulik PhD4,9,10 | Nadia Micali MD, PhD5,6,11
What’s a polygenic risk score?

Weighted Sum of Risk Alleles
Discovery sample → Identification of genomic variants associated with a trait

Polygenic score
Measure of polygenic load

Independent target sample with genetic & phenotype information

Higher polygenic load / propensity

Eating disorder or Control
### Eating Disorder Cases

#### Mental health questionnaire (n = 156,465) & ICD-10 diagnoses

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anorexia nervosa</td>
<td>768</td>
</tr>
<tr>
<td>Bulimia nervosa</td>
<td>423</td>
</tr>
<tr>
<td>Binge-eating disorder</td>
<td>561</td>
</tr>
</tbody>
</table>

| Controls                     | 15,500 |
Genomic Topography of Eating Disorders

Polygenic Scores Associated with Eating Disorders in the UKBiobank – All Traits
Polygenic Scores Associated with Eating Disorders in the UKBiobank – Psychiatric Traits

Outcome: Binge-eating disorder (n = 561) • Bulimia nervosa (n = 423) • Anorexia nervosa (n = 768)

Psychiatric & behavioral polygenic scores:
- Schizophrenia (PGC1)
- PTSD
- Obsessive compulsive disorder
- Migraine
- Major depressive disorder (PGC2)
- Lifetime cannabis use
- Education years
- Borderline personality disorder
- Bipolar disorder (PGC2)
- Autism spectrum disorder
- Anxiety disorders
- Anorexia nervosa (PGC2)
- Alcohol dependence
- ADHD

Odds Ratio (OR) per standard deviation (SD) increase of polygenic scores
Polygenic Scores Associated with Eating Disorders in the UKBiobank – Metabolic Traits

Outcome
- Binge-eating disorder (n = 561)
- Bulimia nervosa (n = 423)
- Anorexia nervosa (n = 768)

B
Type 2 diabetes 2017
Insulin resistance
HDL cholesterol
Fasting insulin (BMI-adjusted)

Odds Ratio (OR) per standard deviation (SD) increase of polygenic scores
Polygenic Scores Associated with Eating Disorders in the UKBiobank – Anthropometric Traits

Outcome: Binge-eating disorder (n = 561), Bulimia nervosa (n = 423), Anorexia nervosa (n = 768)

Anthropometric:
- Waist circumference
- Overweight
- Obesity class 3
- Obesity class 2
- Obesity class 1
- Hip circumference
- Height 2014
- Extreme BMI
- Childhood obesity
- BMI male
- BMI female
- BMI
- Age at menarche

Odds ratio (OR) per standard deviation (SD) increase of polygenic score
One Size Does Not Fit All Eating Disorders

- AN, BN, and BED broadly similarly associated with PRS for psychiatric traits
- Differences lie in PRS for metabolic and anthropometric traits
- Might we be able to use PRS in risk models to predict diagnostic crossover and outcome?
Utility of PRS…

- Can we improve risk assessment by combining PRS with other measures of risk?
- Can we use PRS to screen for mental health disorders in the population?
- Can PRS help in making a diagnosis or clinical decisions?
- Are psychiatric PRS associated with treatment response?
- Are PRS associated with adverse physical health outcomes in mental illness? (e.g., weight gain with antipsychotic medication)
Translating Information for Clinicians, Families, and Patients
Science communication

- Anti-truth and anti-science are rampant
- Scientists’ responsibility to interpret and contextualize
- Clinicians’ responsibility to have general understanding and assist patients & families
- Important role for genetic counseling!
A relatable model

Genetic Risk
Genetic Protective
Environmental Risk
Environmental Protective
A relatable model

Genetic Risk  Genetic Protective  Environmental Risk  Environmental Protective
Role of Genetic Counseling

Genetic counseling for mental illnesses has been shown to help:

• Alleviate stigma and shame
• Correct misconceptions about the condition
• Prepare family members to intervene
• Promote help-seeking behaviors
• Only one study on eating disorders...
  • 107 individuals with personal history of an ED
  • All overestimated risk to female offspring
  • Many had altered reproductive plans

Julianne Michael, UNC-G
PMID: 32666600
Our responsibility

- It is our responsibility not just to do the science, but to package the information for patients and families.
- Clinicians should make an effort to integrate genetics into their own case conceptualizations and develop comfort with answering their patients’ questions.
- Know your limits! If you live in a country with genetic counseling, make use of your colleagues. If not, find resources for your patients.
- Don’t perpetuate misinformation.
Messaging Do’s and Don’t’s

- Genetics is just one piece of the risk puzzle
- All or nothing thinking (genes OR environment; nature OR nurture)
- Challenges understanding probabilities
- Genetic destiny
- Genetic guilt
- Eating disorders are genetic not psychological
- Genetic simplification (I have THE gene[s] for eating disorders)
- Genetic testing…NO!
Now!
Anorexia Nervosa
Bulimia Nervosa
Binge-Eating Disorder
ARFID (pending)
Atypical AN (SE, UK, AU)
What’s New About EDGI?

- Global goal **100K**
- NIMH (US, New Zealand, Australia, and Denmark)
- Plus, the United Kingdom and Sweden
- Coming soon: Mexico, the Netherlands, Puerto Rico, Taiwan, Italy, & more!
- Same questionnaires around the world
- Diversifying samples!
- Digital consent and questionnaires
- Simple at-home saliva collection (COVID-safe!)
- Engaging advocacy community
- **Engaging clinicians!**

www.edgi.org
EDGI Domains: Genes **AND** Environment

- Treatment
- Life events
- Trauma
- Physical Activity
- OCD
- Alcohol & Drug Use
- Tobacco Use
- Anxiety
- Depression
To what end?

- Understand shared and unique biology of AN, BN, BED (some countries including atypical AN and ARFID)
- De-stigmatization
  - Campaign raising awareness and understanding
  - Participant feedback very positive (resonates with their experience)
- Predict likely course of illness and tailor treatment accordingly
- Move toward personalized medicine approach to treatment instead of “one-size-fits-all”
- Drug repositioning or development based on genetic results
- Creation of large participant legacy for research re-contact
- Eliminate mortality
EDGI Launches

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EDGI Talks: YouTube Channel “EDGI Study”
You Can Help! Please Amplify, Follow, & Like Us!

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