The Science Behind (some of) the Academy for Eating Disorders Nine Truths

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Disclosures

- Shire Pharmaceuticals (grant recipient)
- Ironshore (consultant)
- Pearson (author)
- Walker (author)
Gratitude

NIMH
NICHD
Swedish Research Council
Klarman Family Foundation
Wellcome Trust
Foundation of Hope
Academy for Eating Disorders
Global Foundation for Eating Disorders
American Foundation for Suicide Prevention
Davis Foundation
NINE TRUTHS ABOUT EATING DISORDERS

Truth #1: Many people with eating disorders look healthy, yet may be extremely ill.

Truth #2: Families are not to blame, and can be the patients’ and providers’ best allies in treatment.

Truth #3: An eating disorder diagnosis is a health crisis that disrupts personal and family functioning.

**Truth #4:** Eating disorders are not choices, but serious biologically influenced illnesses.

Truth #5: Eating disorders affect people of all genders, ages, races, ethnicities, body shapes and weights, sexual orientations, and socioeconomic statuses.

Truth #6: Eating disorders carry an increased risk for both suicide and medical complications.

**Truth #7:** Genes and environment play important roles in the development of eating disorders.

**Truth #8:** Genes alone do not predict who will develop eating disorders.

Truth #9: Full recovery from an eating disorder is possible. Early detection and intervention are important.

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Produced in collaboration with Dr. Cynthia Bulik, PhD, FAED, who serves as distinguished Professor of Eating Disorders in the School of Medicine at the University of North Carolina at Chapel Hill, “Nine Truths” is based on Dr. Bulik’s 2014 “9 Eating Disorders Myths Busted” talk at the National Institute of Mental Health.

Leading associations in the field of eating disorders also contributed their valuable input.

Truth #4. Eating disorders are not choices, but serious biologically influenced illnesses.
Truth #7. Genes and environment play important roles in the development of eating disorders.
What’s Intriguing About Anorexia Nervosa?

• **Starvation** is reinforcing, anxiolytic, and euphorogenic.

• **Activity** is more reinforcing than food.

• **Satiety** is unpleasant.

• **Fats** are aversive.

• Acutely ill individuals with AN do not exhibit “sickness behaviors.”

• **Until** we renourish them!
Paradoxical Response to Negative Energy Balance

Energy consumed

Energy expended

- Exercise
- Physical activity
- Rest
- Fidgeting
- Purging
Contributing Factors?

Genomics
Intestinal Microbiota
Genomics
Genomics: Why?

Family Studies:
Eating disorders run in families

Twin Studies:
Heritability of AN ~50-60%

Our discovery tools have improved
Psychiatric Genomics Consortium (PGC)

> 800 Investigators

38 Countries

900,000 Samples

Open, Inclusive, Participatory, Democratic

What is the PGC?

The purpose of the Psychiatric Genomics Consortium (PGC) is to unite investigators around the world to conduct meta- and mega-analyses of genome-wide genomic data for psychiatric disorders. This website provides information about the organization, implementation, and results of the PGC.

The PGC began in early 2007 and has rapidly become a collaborative confederation of most investigators in the field. The PGC includes over 800 investigators from 38 countries. There are samples from more than 900,000 individuals currently in analysis, and this number is growing rapidly. The PGC is the largest consortium and the largest biological experiment in the history of psychiatry.

The PGC is passionate about open, inclusive, participatory, and democratic science. Given the importance of the problems we study, we are committed to rapid progress.
Eating Disorders Working Group of the PGC

> 100 Investigators
20 Countries
~20,000 Samples

Co-Chairs
Bulik: UNC/KI
Breen: KCL

PGC Workgroups
- Attention Deficit Hyperactivity Disorders
- Anorexia Nervosa & Eating Disorders
- Autism Spectrum Disorders
- Bipolar Disorders
- Copy Number Variation Group
- Cross-Disorder Group
- Major Depressive Disorders
- OCD & Tourettes Syndrome
- Post Traumatic Stress Disorders
- Schizophrenia
- Substance Use Disorders
- Pathway Analysis Group
The Past Was Dark

BDNF  OPRD1  HTR2A

ESR1  DRD2

10
We Have Emerged from the Darkness!

Candidate Gene Association

- Cases versus Controls
- 1 or a few markers
- Prior knowledge/guesswork essential
- Samples in the hundreds

GWAS

- Cases versus Controls
- ~1,000,000 genetic markers
- No prior knowledge; no guesswork
- Samples in the thousands, tens of thousands, or hundreds of thousands
How to Read a Manhattan Plot

Significance level

$5 \times 10^{-8}$

Chromosome
Size Matters

*The Story of Schizophrenia*
Schizophrenia 2009

ISC 2009
3K cases
PGC1
9K cases

PGC1 + Sweden
14K cases
22 loci
PGC1
9K cases

PGC1 + Sweden
14K cases

PGC2
31K cases
78 loci
Anorexia Nervosa GWAS

1,033 AN cases
3,733 controls

PMID: 21079607
Sign Tests

• WTCCC3-GCAN-discovery versus replication

• **76%** SNPs in same direction discovery meta-analysis (binomial p-value = 4 x 10^-6)

• *Larger samples likely to yield findings*

• **OUR QUEST = BOOST SAMPLE SIZE**
<table>
<thead>
<tr>
<th>Country</th>
<th>Cases + Controls</th>
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<td>USA</td>
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Anorexia GWAS July 2016

CHOP/Price + WTCCC3
3,495 / 10,982
Now What?

Genotype the 16,000 samples in the queue

Rinse and repeat

Identify biological pathways

Determine functional significance of identified genes

Develop targeted therapeutics
There’s Valuable Information Below the Red Line!
LD Score Regression

• 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”

An atlas of genetic correlations across human diseases and traits

Brendan Bulik-Sullivan\textsuperscript{1,3}, Hilary K Finucane\textsuperscript{4,9}, Verner Anttila\textsuperscript{1,3}, Alexander Gusev\textsuperscript{5,6}, Felix R Day\textsuperscript{7}, Po-Ru Loh\textsuperscript{1,5}, ReproGen Consortium\textsuperscript{8}, Psychiatric Genomics Consortium\textsuperscript{8}, Genetic Consortium for Anorexia Nervosa of the Wellcome Trust Case Control Consortium\textsuperscript{38}, Laramie Duncan\textsuperscript{1,3}, John R B Perry\textsuperscript{7}, Nick Patterson\textsuperscript{1}, Elise B Robinson\textsuperscript{1,3}, Mark J Daly\textsuperscript{1,3}, Alkes L Price\textsuperscript{1,5,6,10} & Benjamin M Neale\textsuperscript{1,3,10}
### Brainstorm, Anttila et al (under review)

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$r_g = 0.55$
Obesity, BMI, Weight

Glucose, HOMA-Beta, Insulin

HDL measures

Psychiatric

Cognitive performance

-0.5 0.0 0.5
Genetic Correlation

Personality
Psychiatric
Educational
Weight & BMI
Insulin & glucose related
Lipoprotein & cholesterol

Neuroticism (GPC)
Neuroticism (SSGAC)
Schizophrenia (PGC v1)
Schizophrenia (PGC v2)
Cross disorder (PGC v1)
Education years (SSGAC v1)
Education years (SSGAC v2)
College attended (SSGAC)
Extreme BMI
Body fat percentage
Overweight
Obesity class 3
Obesity class 1
BMI (Giant)
BMI
Obesity class 2
Hip circumference
HOMA-IR
Fasting insulin
HOMA-Beta
Fasting glucose
Total cholesterol in large HDL
Free cholesterol in large HDL
Cholesterol esters in large HDL
Total lipids in large HDL
Concentration of large HDL particles
Phospholipids in large HDL
HDL cholesterol
Rethinking

• Positive genetic correlation with OCD no surprise

• Positive genetic correlation between AN and SCZ

• Perceptual distortions

• Cognitive distortions

Psychotic?
Rethinking

• Uncanny ability to achieve low BMI
• Difficulty/inability to gain weight after achieving extreme low weight
• Negative correlations with BMI and other unhealthy metabolic parameters
• Positive correlations with healthy metabolic parameters
• Paradoxical reaction to negative energy balance
• Maintain low BMI even after recovery
Truth #8. Genes alone do not predict who will develop eating disorders.
The Intestinal Microbiota
What is the microbiome?

- **Microbiota**: microbial communities in/on body (almost everywhere)
- **Microbiome**: cumulative genomes of microbiota

> Each individual’s microbiome is unique!
> A bugprint!

Costello et al. (2009)
Intestinal microbiota = the most dense ecosystem on earth!

- Human microbiome: 750,000 genes
- Human genome: 23,000 genes

>30 fold

100+ trillion microbes in the GI tract alone; outnumber human cells at least 3:1

Li et al. (2014)
Basic Principles

• Microbial community contributes to energy harvest from the diet

• How can individuals with AN survive on so little energy?
Characterizing the Microbiome (I)

- Need a unique ID to identify each member of microbial community
- Bacterial “barcode” (unique signature): hypervariable region of 16S ribosomal RNA gene
What About the Gut Microbiota in Anorexia Nervosa?
Enteric Microbe-Gut-Brain Axis

Bacterial Metabolites
SCFA
Neurotransmitters
Other Substrates

Impact on:
Mood?
Behavior?
Metabolism?
Satiety?
Weight?

Energy Restriction
Vagus Nerve

Bravo et al. (2011), Sherwin et al. (2016)
Common Parlance

Trust Your Gut

Gut Instincts

Butterflies in Your Stomach

Sinking Feeling in The Pit of Your Stomach

All Disease Begins in the Gut
Death sits in the bowels

Food for Thought
Characterize Taxonomy and Diversity of Intestinal Microbiotas

- AN T1 < 75% IBW
- AN T2 ~85% IBW
- Healthy Control
Compare Taxa Abundance and Diversity
AN T1 vs. HC
Compare Taxa Abundance and Diversity
AN T2 vs. HC
Compare Taxa Abundance and Diversity
AN T1 vs. AN T2
Demographic & Clinical Characteristics

**Patients with AN (n=16)**

<table>
<thead>
<tr>
<th>Demographic &amp; Clinical Parameters</th>
<th>Mean (SD)</th>
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<tbody>
<tr>
<td>Female</td>
<td>100%</td>
</tr>
<tr>
<td>Age</td>
<td>28.0 (11.7) years</td>
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<tr>
<td>BMI (admission)</td>
<td>16.2 (1.5) kg/m²</td>
</tr>
<tr>
<td>BDI</td>
<td>26.6 (13.4)  → moderate</td>
</tr>
<tr>
<td>BAI</td>
<td>17.7 (11.9)  → moderate</td>
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<tr>
<td>EDE-Q (total)</td>
<td>3.6 (1.8)</td>
</tr>
<tr>
<td>Dietary restraint</td>
<td>3.7 (1.9)</td>
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<tr>
<td>Eating concern</td>
<td>3.4 (1.9)</td>
</tr>
<tr>
<td>Shape concern</td>
<td>3.8 (1.9)</td>
</tr>
<tr>
<td>Weight concern</td>
<td>3.4 (2.1)</td>
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</tbody>
</table>

Note: results are mean (± SD)

Exclusion criteria:
- Age <15 or >64 years
- History of GI surgery
- IBS, IBD, celiac
- Antibiotics/probiotics in the last two months
Alpha (within sample) Diversity

Number of species present

Chao-1 (Number & Relative Abundance)

A diverse microbiota is a healthy microbiota!

Kleiman et al. (2015)
Summary

- Lower richness and diversity in acutely ill AN
- Changes to microbiota may be adaptation to starvation
- Consistent with changes to maximize extraction of energy from the diet
Compare Microbial Measures with Measures of Depression
AN T1 vs. HC
Anorexia: Significant Association Between Depression and Bacterial Diversity

Higher BDI scores $\rightarrow$ lower bacterial diversity

Depression, and eating disorder psychopathology associated with microbial composition/diversity in patients with acute AN

PMID: 26428446
Transplant into Germ-free Mice

AN T1
< 75% IBW

AN T2
~ 85% IBW

Anxiety
Gnotobiotics

*gnostos* 'known'

*bios* 'life'

Isolators

Normal Microbiota

Germ-free

Normal

Microbiota

Germ-free
Cause and Effect

- Extract microbiota from obese and lean donor mice
- Transplant into germ-free mice
- Significant difference in body fat over two weeks
Increased Anxiety in Germ-free Mice

More time in open space = less anxious

Percent time spent in the center of the open field in GF mice and GF mice colonized with HC or AN.
Limitations

• Limited power at the lowest taxonomic levels
• 16S rRNA data describes microbial composition/diversity but not metabolic activity or functional impact
• Did not control for dietary intake
• Unable to compare patients with AN to similarly malnourished individuals without AN
Now What?

- Identify mechanisms of gut-brain axis in animal models (Tarantino/Cryan)
- Moving from asking who’s there (DNA) to what they’re doing (RNA)
- Can specific enteric microbes predict weight maintenance?
- New avenues for therapeutics (targeted probiotics/antibiotics/prebiotics)
  - Improve weight restoration and maintenance
  - Decrease anxiety
  - Reduce discomfort of refeeding
The Ultimate

Relation between host genomics and the intestinal microbiome
Totuus #1: Moni syömishäiriötä sairastava näyttää terveeltä, mutta voi silti olla hyvin vakavasti sairas.

Totuus #2: Perheitä ei pidä syyllistää. Syömishäiriö ei ole perheenjäsenten vika, ja he voivat olla arvokas voimavara hoidossa.

Totuus #3: Syömishäiriö on terveydellinen kriisi, joka häiritsee sekä yksilön että perheen toimintakykyä.

Totuus #4: Syömishäiriöt eivät ole valintoja, vaan vakavia sairauksia, joiden syntymiseen vaikuttavat biologiset tekijät.

Totuus #5: Kuka tahansa voi sairastua syömishäiriöön, riippumatta sukupuolesta, iästä, etnisestä taustasta, ruumiinrakenteesta ja painosta, seksuaalisesta suuntautumisesta tai sosioekonomisesta asemasta.

Totuus #6: Syömishäiriöihin liittyy kohonnut itsemurhariski sekä kohonnut lääketieteellisten komplikaatioiden riski.

Totuus #7: Perintötekijöillä ja ympäristötekijöillä on tärkeä rooli syömishäiriöiden synnyssä.

Totuus #8: Perintötekijät eivät yksin määritteleet sitä kuka sairastuu syömishäiriöön.

Totuus #9: Syömishäiriöstä voi parantua täysin. Varhainen tunnistaminen ja hoito ovat tärkeitä.
Invitation

Twitter
@cbulik

Read our blog:
http://uncexchanges.wordpress.com

And visit my website:
www.cynthiabulik.com