Why look for genes in OCD?

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Outline

1. OCD is genetic
2. We will find OCD genes (I promise)
3. Finding genes could:
   - inform diagnostic conceptualization
   - reveal disorder mechanisms
   - help patients
4. Specific aims
OCD is genetic
Family study

- Queen Elizabeth II
- Philip, Duke of Edinburgh

Charles, Prince of Wales

- Camilla, Duchess of Cornwall
- Captain Mark Phillips
- Diana, Princess of Wales
- Harry, Prince Henry of Wales
- William, Duke of Cambridge
- Kate, Duchess of Cambridge
- Prince George of Cambridge

Anne, Princess Royal

- Vice-Admiral Timothy Laurence
- Prince Peter Phillips
- Autumn Phillips
- Savannah
- Mia Grace

Andrew, Duke of York

- Sarah, Duchess of York
- James, Viscount Severn

Edward, Earl of Wessex

- Sophie, Countess of Wessex

- Divorced

Family tree of the British Royal Family.
Figure 1. Risk for Obsessive-Compulsive Disorder Among Relatives With Differing Genetic and Environmental Distance to All Diagnosed Obsessive-Compulsive Disorder Cases in the Swedish National Patient Register (1969-2009) Compared With Matched Population Control Subjects
Twin study

Helps dissect genetic vs environmental effects
Correlations for self-reported Obsessive-Compulsive Symptoms among 16,383 twins aged 20 to 47 years in the STAGE study, stratified by zygosity and sex.
Brain activation during reversal of responses. Patients with OCD and their unaffected relatives showed under-active brain regions during reversal compared to people with no family history of the condition.

Human trichotillomania gene in mice

Canine compulsive disorder (CCD)

www.boredpanda.com/donald-trump-hair-look-alikes/
Questions?
We will find OCD genes
DNA sources

Blood (white blood cells)  Saliva (WBC & cheek cells)
A Recipe-Genome Analogy

A single recipe is like...

A recipe book is like...

Two copies of 23 recipe books like...

A Gene:
One set of instructions for how to make one protein.

A Chromosome:
Thousands of sets of instructions for how to make thousands of proteins.

Our Genome:
ALL of the sets of instructions for how to make ALL the proteins we need.

ALL (gene, chromosome, genome) are written in same the DNA alphabet!!!
A Recipe-Genome Analogy

In order for scientists to find a specific gene, they need to know which “book” to look in, and which “page” to turn to.
A Recipe-Genome Analogy

http://justsomething.co/the-34-most-hilarious-pinterest-fails-ever/
DNA variation

- Human genome is ~3 billion letters
- Variation:
  - Single nucleotide polymorphism (SNP, ~3 million/person):
  - Copy number variant (CNV, ~10,000/person):
DNA genotyping

- A collection of microscopic DNA spots ("probes") attached to solid surface
- For each SNP, two "probes" present
- ~1 million SNPs/microarray
Inheritance – complex traits

Few “tall” gene variants

Many “tall” gene variants
Association

**cases** (n=1,000) people with heart disease

- **C**: 62%
- **T**: 38%

**controls** (n=1,000) people without heart disease

- **C**: 49%
- **T**: 51%
# Genome-wide association study (GWAS)

## SNP1

**Cases**
- Count of G: 2104 of 4000
- Frequency of G: 52.6%

**Controls**
- Count of G: 2676 of 6000
- Frequency of G: 44.6%

**P-value:** $5.0 \cdot 10^{-15}$

## SNP2

**Cases**
- Count of G: 1648 of 4000
- Frequency of G: 41.2%

**Controls**
- Count of G: 2532 of 6000
- Frequency of G: 42.2%

**P-value:** 0.33

*Repeat for all SNPs*
Genome-wide association study (GWAS)

“Manhattan plot”
Genome-wide association study (GWAS)

“Manhattan plot”
Schizophrenia GWAS: 2009

Cases: 2,601
Controls: 3,345
Hits: 0

Common polygenic variation contributes to risk of schizophrenia and bipolar disorder

“Omaha plot”
Schizophrenia GWAS: 2011

Cases: 9,394
Controls: 12,462
Hits: 5

Genome-wide association study identifies five new schizophrenia loci

*Nature Genetics* 43, 969–976 (2011)
Schizophrenia GWAS: 2012

Cases: 27,785
Controls: 28,441
Hits: 62

Genome-wide association analysis identifies 13 new risk loci for schizophrenia

Nature Genetics 45, 1150-1159 (2013)
Schizophrenia GWAS: 2014

Cases: 35,476
Controls: 46,839
Hits: 108

Schizophrenia GWAS: 2014

Dopamine (current pharmacotherapy)

DRD2
Psychiatric GWAS: lessons learned

- Large, well-phenotyped samples key!
- Many genes involved
- Even genes of small effect can be important:
  - Schizophrenia: *DRD2* variant increase risk just 10%, yet all antipsychotics bind to this receptor
  - Cholesterol: *HMGCR* variant increases cholesterol just 5%, yet statins (best selling drug in the world) inhibit this enzyme
Questions?
Finding genes could...
Inform diagnostic conceptualization

Obsessive-Compulsive and Related Disorders
Obsessive-Compulsive Disorder
Body Dysmorphic Disorder
Hoarding Disorder
Trichotillomania (Hair-Pulling Disorder)
Excoriation (Skin-Picking) Disorder
Reveal disorder mechanisms

The New York Times

Scientists Move Closer to Understanding Schizophrenia’s Cause

By BENEDICT CAREY  JAN. 27, 2016

An image from a fluorescent microscope showing C4 proteins, in green, located at the synapses in a culture of human neurons. Heather de Rivera/McCarroll Lab/Harvard, via Associated Press

Help patients

- identify at-risk individuals
- promote earlier intervention
- help with differential diagnosis
- help guide treatment choices
- lead to rational drug development
Specific aims
Funded by VR

**Aim 1** Collect case DNA & phenotypes (years 1-3)
Available at no cost

- OCD
  - N = 3,000
- Controls
  - N = 8,000

All SNP genotyped, 1,000 whole genome sequenced

**Aim 2** Discover risk genes & pathways (years 3-4)

- Genotype all 3,000 cases; whole genome sequence 500 cases
- Known risk genes from dogs
- Human replication samples
  - 5,000 cases & 5,000 controls

High-confidence, replicated risk genes & pathways

**Aim 3** Identify gene by environment effects (years 4-5)

- Environment
- Epidemiology
- Risk genes & pathways
- Treatment [CBT, , ]
Pending @ NIH

**Aim 1** Collect case DNA & phenotypes
- **OCD**
  - N = 10,000
  - Available at no cost
  - All SNP genotyped, 1,000 whole genome sequenced

**Aim 2** Discover risk genes & pathways
- GWAS: 10,000 cases
  - Known risk genes from dogs
  - Human replication samples
    - 8,000 cases, 5,000 controls

**Aim 3** Integrate genetic and register data
- Genetic risk score (GRS)
- Environment
- Epidemiology
- Treatment
  - CBT
THANKS!