OCD: Using Genome Data to Predict Risk, Symptoms and Treatment Response

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DISCLOSURE

- No conflict of interest
• No conflicts of interest to disclose

• Co-Lead of University of Toronto’s Psychiatry Residency Psychopharmacology Curriculum

• Service Lead, OCD/Anxiety Disorders Services at CAMH

• Salary: University of Toronto Academic Scholars Award

• Grants: BBRF NARSAD Young Investigator Grant, Physicians’ Services Incorporated grant, Labatt internal grant, and International OCD Foundation Young Investigator Grant
Learning Objectives

1. Understand the heterogeneity and complexity of OCD

2. Understand genetic approaches to examine the potential role of brain genes in OCD risk and antidepressant response

3. Identify genetic variations that contribute to the risk of developing OCD and predicting antidepressant response
Presentation Outline

- OCD
- Genetic Rationale
- GWAS
- Pharmacogenetics
- Future Plans
- Acknowledgement & Questions
Obsessive-Compulsive Disorder (OCD)

- Anxiety disorder in DSM-IV (APA, 2000)
- OCD and related disorders in DSM-5 (APA, 2013)
- Complex, chronic, & severe
- 1-3% of the general population (APA, 2000)

Characterized by (APA, 2000):

- Obsessions = recurring and persistent unwanted thoughts or images
- Compulsions = rituals or repetitive acts performed to reduce anxiety
Fear of germs

Thinking that something bad is going to happen to you

Thinking something bad is going to happen to someone you love

Thinking that you might harm someone even though you don’t want to
OCD Symptoms

- Contamination
- Symmetry
- Aggressive
- Religious
- Somatic
- Hoarding
- Sexual
- Checking
- Washing
- Repeating
- Ordering
- Counting

Biopsychosocial Model: Etiology of OCD

Predisposing Factors:
- Genetics

Precipitating Factors:
- Identity, Self-Esteem

Perpetuating Factors:
- Family, Vocation

Stressors

Repetitive acts or rituals to alleviate anxiety
"Genetics play a large part in it ... for example, if your parents didn't have any children you won't either!"
Family Studies
Family Studies of OCD

- Obsession & compulsions = highly familial (Pauls, 2010)
  - 9% with positive family history vs 2%
  - 16-24% of 1st degree relatives with OCD and/or OC behaviours
  - 11-23% child onset
  - 10% adult onset (3-17% range)

- INABILITY to differentiate between genes or environment
Twin Studies

**Regular Siblings**
- Sibling 1
- Sibling 2
- 50% similar

Regular siblings are conceived during different pregnancies.

**Fraternal (Dizygotic) Twins**
- Twin 1
- Twin 2
- 50% similar

Fraternal twins are also the product of two different sperms and eggs, but are conceived during the same pregnancy.

**Identical (Monozygotic) Twins**
- Twin 1
- Twin 2
- 100% genetically similar

Identical twins are conceived during the same pregnancy, with only one sperm and one egg that split apart to form separate embryos.
Twin Studies of OCD

Heritabilities from twin studies (Carey & Gottesman, 2000; van Grootheest et al., 2005; Pauls, 2010)

- OCD = 27-53% (71% for hoarding)
- Obsession = 26%
- Compulsion = 33%
- Monozygotic twins = 80-87%
- Dizygotic twins = 47-50%
- Children = 56-65%
- Adult = 27-47%
Case-Control Study Design

### Association Studies

**OCD Patients**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>OCD</th>
<th>Controls</th>
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<td>24</td>
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<table>
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<th>Genotype</th>
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<tr>
<td>DRD2 allele 2</td>
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</table>

$\chi^2 = 5.377$  
$p < 0.025$
The A allele is transmitted to resistant or susceptible offspring three times out of four.
Family Studies of OCD

- Obsession & compulsions = highly familial (Pauls, 2010)
  
  - 9% with positive family history vs 2%
  
  - 16-24% of 1st degree relatives with OCD and/or OC behaviours
  
  - 11-23% child onset
  
  - 10% adult onset (3-17% range)

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Twin Studies of OCD

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- Children = 56-65%
- Adult = 27-47%
Where do we look?
Genetics Rationale

- Strong genetic component (Nicolini et al., 2009)
- Multiple small gene effects
- Multi-factorial with biological, psychological, and socio-cultural factors
- Pharmacotherapy of OCD (CPA, 2006)
  - SSRI antidepressants as first-line treatment
  - Atypical antipsychotics as first-line augmenting agents
  - NMDA modulators as second-line augmenting agents (i.e., memantine, topiramate), as shown in preclinical trials (Hollander et al., 2006; Van Ameringen et al., 2006), animal models (Egashira et al., 2008), and clinical trials (http://clinicaltrials.gov/ct2/show/NCT01371110)
Adapted from: Pato et al. (2002) *J Clin Psychiatry* 63(Suppl. 6):30-3
Table 1. Main meta-analysis: weighted mean ORs significantly > 1 (highlighted in bold) indicate that the target allele was associated with obsessive-compulsive disorder

<table>
<thead>
<tr>
<th>Gene</th>
<th>Polymorphism</th>
<th>Target allele vs other allele(s)</th>
<th>No. of data sets</th>
<th>Mean OR (and 99th percentile confidence interval)</th>
<th>Obtained P-value for mean OR</th>
<th>Holm-critical P-value</th>
<th>Mean OR expressed as Cohen’s $d$</th>
<th>$I^2$ (%)</th>
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<tbody>
<tr>
<td>5-HTT</td>
<td>STin2 VNTR</td>
<td>12 vs non-12</td>
<td>11</td>
<td>1.052 (0.845–1.309)</td>
<td>0.554</td>
<td>0.006</td>
<td>0.028</td>
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<tr>
<td>5-HTTLPR</td>
<td>Coded as biallelic</td>
<td>$L$ vs $S$</td>
<td>34</td>
<td>1.051 (0.937–1.179)</td>
<td>0.266</td>
<td>0.005</td>
<td>0.027</td>
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<tr>
<td>5-HTTLPR</td>
<td>Coded as triallelic</td>
<td>$L_a$ vs ($L_0 + S$)</td>
<td>8</td>
<td>1.251 (1.048–1.492)</td>
<td>0.001</td>
<td>0.003</td>
<td>0.123</td>
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<tr>
<td>COMT</td>
<td>rs265</td>
<td>Met vs Val</td>
<td>12</td>
<td>1.013 (0.765–1.342)</td>
<td>0.904</td>
<td>0.017</td>
<td>0.007</td>
<td>56</td>
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<tr>
<td></td>
<td>rs4680</td>
<td>Met vs Val</td>
<td>25</td>
<td>1.200 (1.001–1.438)</td>
<td>0.010</td>
<td>0.003</td>
<td>0.101</td>
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<td>DAT1</td>
<td>VNTR</td>
<td>9 vs non-9</td>
<td>8</td>
<td>1.260 (0.894–1.775)</td>
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<td>0.003</td>
<td>0.127</td>
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<td>rs1800497</td>
<td>C vs $T$</td>
<td>7</td>
<td>0.801 (0.535–1.198)</td>
<td>0.156</td>
<td>0.004</td>
<td>0.122</td>
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</table>

Meta-analysis of association between OCD & the 3’ region of neuronal glutamate transporter gene $SLC1A1$

- Stewart et al. (2013) 162B(4):367-379
- Am J Med Genet B Neuropsychiatr Genetic

NEGATIVE STUDY
Genome-Wide Association Study

- Population resources - trios or case-control samples
- Whole-genome genotyping
- Genome-wide association
- Fine mapping
- Gene mining
- Gene sequencing & polymorphism identification
- Identification of causative SNPs
- Pathway analysis & target identification
Manhattan (Toronto) Plot

Toronto CN Tower
IOCDFGC N = 1,465 cases, 5,557 controls, 400 trios
No GWAS significance -> only reached $P=10\times10^{-6}$

**Top Hits:**

- **BTBD3** (BTB/POZ domain containing 3) = 20p12.2
- **DLGAP1** (homolog-associated protein 1) = 18p11.31
- **FAIM2** (fas apoptotic inhibitory molecule 2) = 12q13.12
- **GRIK2** (glutamate receptor 2) = 6q16.3
- **FUT2** (fucosyltransferase 2) = 19q13.33
- **ADCY8** (adenylate cyclase 8) = 8q24.22
OCGAS N = 1,065 families (1,406 cases), 1,984 controls
No GWAS significance -> only reached $P = 4.13 \times 10^{-7}$

Top Hits:
- **PTPRD** (protein tyrosine phosphatase receptor type D) = 9p23
- **CDH9** (cadherin 9) = 5p15
- **CDH10** (cadherin 10) = 5p15
- **IL7** (interleukin 7) = 8q21.13

Meta-analysis N = 2,688 cases and 7,037 controls
No GWAS significance -> only reached $P=7.1\times10^{-7}$

Top Hits:
- **CASC8/11** (cancer susceptibility 8/11) = 8q24.21
- **GRID2** (glutamate ionotropic receptor delta type subunit 2) = 4q22.1
- **KIT** (KIT proto-oncogene receptor tyrosine kinase) = 4q12
Obsessive-Compulsive Behaviours:

1) NTR GWAS N = 6,931 individuals
- 1 GWAS significance -> *MEF2BNB* (*P*=2.56x10⁻⁸)
  - *MEF2BNB* (myocyte enhancer factor 2B) = 19p13
  - den Braber et al. (2016) Transl Psychiatry 6:731

2) Spit for Science GWAS N = 15,880 youths
- 1 GWAS significance -> *PTPRD* (*P*=2.48x10⁻⁸)
  - *PTPRD* (protein tyrosine phosphatase receptor type D) = 9p23
  - Burton et al. (2021) Transl Psychiatry 11(1):91
OCD

Gene

A
B
C
D
E
F
G
H
I

+Family History

Symptom severity

Early Onset

Checking

Bad thoughts

Cognitive deficit(s)

Drug response

Cleaning

Hoarding

Drug tolerability
OCD Sample

- Clinical characteristics of OCD = highly heterogeneous
- Clinical Phenomenology of OCD
  - Gender
  - Age at onset (AAO; first met diagnosis)
  - Y-BOCS symptom checklist
  - Psychiatric comorbidities (SCID-IV)
  - Family history of OCRDs (FHI)
  - SRI response
- N=560 OCD participants & 273 family members
Gender

- **Insidious onset**
- **Chronic course**
- ↑ severity
- ↑ aggressive, sexual, religious, checking, ordering, hoarding

- **SLC1A1** (Arnold et al., 2006; Dicketl et al., 2006; Shugart et al., 2009; Stewart et al., 2007)
- **BDNF** (Hemmings et al., 2006; 2008)
- **COMT** (Hemmings et al., 2006; Liu et al., 2011; Pooley et al., 2007)

- **Abrupt onset**
- **Episodic course**
- ↓ severity
- ↑ contamination, cleaning, somatic symptoms

- **BDNF** (Hemmings et al., 2009; Katerberg et al., 2009; Márquez et al., 2013)
- **NTRK2** (Alonso et al., 2008)
- **COMT** (Katerberg et al., 2010; Liu et al., 2011)

References: de Mathis et al., 2011; Jaisoorya et al., 2009; Nestadt et al., 1998; Rosso et al., 2012; Tukel et al., 2013
Age At Onset (AAO)

**Early ≤ 10-18**
- ↑ Tourette’s syndrome
- ↑ ADHD symptoms and BD
- ↑ family history of OCD
- ↑ symptom severity
- ↑ impairment and ↓ prognosis

**Late ≥ 17-30**
- Acute onset
- Episodic course
- ↑ rates of GAD and MDD
- ↑ frequency of panic attacks

**Genetic Factors**
- **SLC6A4** (Bloch et al., 2008; Walitza et al., 2014)
- **HTR2A** (Denys et al., 2006; Walitza et al., 2002; 2012)
- **SLC1A1** (Dickel et al., 2006; Wu et al., 2013)
- **SLC1A1** (Dallaspezia et al., 2014)
- **NTRK2** (Alonso et al., 2008)
- **COMT** (Katerberg et al., 2010; Liu et al., 2011)

**References:** de Mathis et al., 2011; Jaisoorya et al., 2009; Narayanaswamy et al., 2012; Nestadt et al., 1998; Rasmussen & Eisen, 1992
SRI Response

Responders
- Insidious and later onset
- Intermittent course of illness
- Less severe
- Absence of previous treatment

Non-Responders
- Earlier onset
- Hoarding symptoms
- ↓ insight
- Depression

- **SLC1A1** (Real et al., 2010)
- **HTR2A** (Corregiari et al., 2013; Denys et al., 2017; Zhang et al., 2004)
- **BDNF** (Real et al., 2009)
- **SLC6A4** (McDougle et al., 1998; Denys et al., 2007)
- **COMT** (Liu et al., 2011; Michaelovsky et al., 2008)

References: Marazziti and Consoli, 2010
1. QuantStudio

- 833 Subjects:
  - 497 OCD
  - 336 Family Members

Programs: PLINK 1.07, Haploview 3.32, SPSS 20.0, Unphased 3.1.7

Phenotypes: Gender, AAO, Y-BOCS severity & symptom dimensions, Comorbidity, Family Hx

2. GWAS

- 406 Subjects:
  - 251 OCD
  - 155 Family Members

After QC

Programs: PLINK 1.07 (qfam), LocusZoom 1.1

Variables: AAO, Y-BOCS

3. SRI Response

- 497 Subjects:
  - 217 Caucasian OCD

SRI Response: CGI-I

Responders: ≥1 SRI, very much & much improved
Non-responders: ≥2 SRIs, minimal, no change, or worse
Age At Onset (AAO) Three Normal Distributions

Admixture Analysis
- STATA 11.0
- Denormix module
Age At Onset (AAO)

Early $\leq 8$
- $\uparrow$ symmetry/order
- $\uparrow$ contamination/cleaning symptoms

Intermediate 9-17

Late $\geq 18$
- $\downarrow$ symmetry/order symptoms
- $\downarrow$ contamination/cleaning symptoms

$FUT2$ rs681343: $\uparrow$ T allele/TT genotype in early-onset

$COMT$ rs4818: $\uparrow$ G allele in late-onset
1. QuantStudio

833 Subjects:
- 497 OCD
- 336 Family Members

**Programs:** PLINK 1.07, Haploview 3.32, SPSS 20.0, Unphased 3.1.7

**Phenotypes:** Gender, AAO, Y-BOCS severity & symptom dimensions, Comorbidity, Family Hx

2. GWAS

406 Subjects:
- 251 OCD
- 155 Family Members

After QC

297 Subjects:
- 203 OCD
- 97 Family Members

**Programs:** R 3.0.2, PLINK 1.07 (qfam), LocusZoom 1.1

**Variables:** AAO, Y-BOCS

3. SRI Response

497 Subjects:
- 217 Caucasian OCD

**Programs:** PLINK 1.07, R 3.0.2, SPSS 20.0

**SRI Response:** CGI-I

**Responders:** $\geq 1$ SRI, very much & much improved

**Non-responders:** $\geq 2$ SRIs, minimal, no change, or worse
Manhattan Plot for AAO (left) & Y-BOCS (right) prior to Permutation N=406 (222 after QC)
Pharmacogenetics

Antidepressant’s mechanism of action involves 5HT, DA, and glutamate.

~40-60% of patients do not respond to antidepressants and clinical/demographics factors only modestly influence drug response.

Encyclopedia of DNA Elements (ENCODE) project reported 80.4% of human genome displaying some functionality into gene regulation, gene-gene and gene-environment interaction (Kavanagh et al., 2010; Nair & Howard, 2013)
Pharmacodynamics

Dopamine, Serotonin, etc.

Environmental Factors

Response & Side Effects

CYP1A2, CYP2D6, etc.

Pharmacokinetics

sex, diet, smoking, exercise, ethnicity, age, psychosocial
Poll of 900 medical students and undergrads:

90% Agreement for Pharmacogenetic Testing

Zai et al. (2014)
Your DNA Affects Your Response to Drugs

DNA Test

Safe, effective  Safe, not effective  Unsafe, not effective  Unsafe, effective
Limited number of studies without robust findings or replication
Replication Study:

N = 112 OCD cases
- SRI responder = “moderate improvement” or “total remission”
- SRI non-responder = “no response” or “minimal response”
- Excluded “could not tolerate” and missing data
- \( DISP1 \) = Dispatched RND Transporter Family Member 1
- \( rs17162912 \) near \( DISP1 \) gene -> negative \( (P=0.32) \)
1. QuantStudio

- 833 Subjects: 497 OCD, 336 Family Members

**Programs:** PLINK 1.07, Haploview 3.32, SPSS 20.0, Unphased 3.1.7

**Phenotypes:** Gender, AAO, Y-BOCS severity & symptom dimensions, Comorbidity, Family Hx

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- 297 Subjects: 203 OCD, 97 Family Members

**Programs:** R 3.0.2, PLINK 1.07 (qfam), LocusZoom 1.1

3. SRI Response

- 497 Subjects: 217 Caucasian OCD

**Programs:** PLINK 1.07, R 3.0.2, SPSS 20.0

**SRI Response:** CGI-I

**Responders:** ≥1 SRI, very much & much improved

**Non-responders:** ≥2 SRIs, minimal, no change, or worse
**AIM:**
- Genetic variations may predict antidepressant response in OCD

**METHOD:**
- 497 DSM-IV OCD subjects (SCID-IV & Y-BOCS severity score)
- SSRIs (fluoxetine, fluvoxamine, sertraline, paroxetine, citalopram) and clomipramine
- Drug response: CGI-I
  - Responders = “very much” and “much” improved
  - Non-responders = “minimal”, “no change”, or “worse”
- Exclusion criteria: bipolar/psychotic/neurological disorders
- 32 SNPs: MAF>1%, ENCODE databases
- Genotyping: 32-SNP custom-made chip (Life Technologies ®)
- Statistics: PLINK, R program, SPSS
## QuantStudio Subject Demographics

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<th>Chromosome</th>
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### Descriptors

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<td>N</td>
<td>217</td>
<td>N/ Mean (S.D.)</td>
</tr>
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<td>Age (N=191)</td>
<td>37.6 (11.9)</td>
<td>Gender (N=197)</td>
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<td>Gender (N=197)</td>
<td>57.9% female</td>
<td>Ethnicity</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>100% Caucasian</td>
<td>Age of onset (N=179)</td>
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<td>Age of onset (N=179)</td>
<td>14.6 (9.2)</td>
<td>Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) severity score (N=193)</td>
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QuantStudio 30 SNPs across 14 candidate genes
Any SRI/SSRI Response in OCD

N=106

P=0.002

Any SRI

Any SSRI

-Log10 P Value

HTR1B

FAIM2

HTR2A

Nyholt & Bonferroni: P<0.002
FAIM2  HTR2A  HTR1B  SLC1A1  BDNF  GRIN2B  DLGAP1  FUT2  COMT

+FH OCRDs

+FH OCD

+FH TTM

+FH BDD

Symmetry/Order/Repeat/Checking

Somatic

Comorbid Mood, Anxiety, & OCRDs

Contamination/Cleaning

Aggressive

Comorbid OCRDs

Early Onset

SRI Response

OCD

GENES

Early Onset

Symmetry/Order/Repeat/Checking

Somatic

Comorbid Mood, Anxiety, & OCRDs

Contamination/Cleaning

Aggressive

Comorbid OCRDs

Early Onset

SRI Response

OCD
OCD Genetics Summary

- OCD = highly heterogeneous and complex
  - Clinical Heterogeneity with subtype analysis
  - Ethnicity heterogeneity with PCA from GWAS data
- Most promising results from these following systems:
  - Serotonin (5HT) = $HTR1B$, $HTR2A$
  - Glutamate (Glu) = $SLC1A1$, $GRIN2B$, $DLGAP1/2$, $GRIK$
- Limitations:
  1. Sample size
  2. Multiple comparisons
- Gene-gene & gene-environment interaction
Future Directions

» Additional phenotypes
  » Cognitive deficits/impairments including cognitive inflexibility and motor dysinhibition (BBRF NARSAD Young Investigator Grant)
  » Treatment response including CBT and MBCT (CIHR Project Grant in preparation for September 2021)

» Different approaches
  » Cross-disorder to examine cognitive measures including executive dysfunction (BBRF NARSAD Young Investigator Grant) and antidepressant response (Brain Canada submitted; NIMH Grant in preparation)
  » Epigenetic biomarkers in predicting disease risk and treatment response (PSI and IOCDF Young Investigator Grant)
“Each capsule contains your medication, plus a treatment for each of its side effects.”
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