PGC Worldwide Lab Call Details

DATE: Friday, May 8th, 2015

PRESENTER: Patrick F. Sullivan, MD, FRANZCP, from UNC-CH and KI

TITLE: “Planning the PGC3 grant: Talk #2.”

START: We will begin promptly on the hour.

1000 EDT - US East Coast
0700 PDT - US West Coast
1500 BST - UK
1600 CEST - Central Europe
2400 AEST – Australia (Midnight into Saturday, May 9th, 2015)

DURATION: 1 hour

TELEPHONE:

- US Toll free: 1 877 703.6109
- International direct: +1 617 399.5126
- Toll-free number? See http://www.btconferencing.com/globalaccess/?bid=288_attended
- Operators will be on standby to assist with technical issues. “*0” will get you assistance.
- This conference line can handle up to 300 participants.

PASSCODE: 188 641 29

Lines are Muted **NOW**

Lines have been automatically muted by operators as it is possible for just one person to ruin the call for everyone due to background noise, electronic feedback, crying children, wind, typing, etc.

Operators announce callers one at a time during question and answer sessions.

Dial *1 if you would like to ask a question of the presenter. Presenter will respond to calls as time allows.

Dial *0 if you need operator assistance at any time during the duration of the call.

UPCOMING PGC Worldwide Lab

DATE: **Friday, June 12th, 2015**
PRESENTER: Benjamin Neale, PhD, from Harvard Medical School, ATGU MGH, and Broad Institute.
TITLE: To Be Announced
START: We will begin promptly on the hour.

1000 EDT - US East Coast
0700 PDT - US West Coast
1500 BST - UK
1600 CEST - Central Europe
2400 AEST – Australia (Midnight into Saturday, June 13th, 2015)

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PASSCODE: 188 641 29

Planning the PGC3 grant
Talk #2

8 May 2015

PF Sullivan (UNC-Chapel Hill & Karolinska Institutet)

Today

- *A chance for information, discussion, to provide feedback, ideas, get involved*
- *Hard to do by phone!*
- *Requires active involvement – do either:*
  - *Ask a question: dial *1*
  - *Send an email to sswillia@email.unc.edu*

Executive Summary

- *Initially for March. Delayed to June to add 2 EUR sites*
- *This is mostly a data analysis grant*

- PGC:
  - Mature, amazing "brain trust", exceptional progress
  - We now have a logical path to knowledge
  - We could do (a lot) more

- *Key theme – "PGC: Finding actionable variation"*
  - *Biology (rare & common)*
  - *Clinical*
  - *Therapeutic*

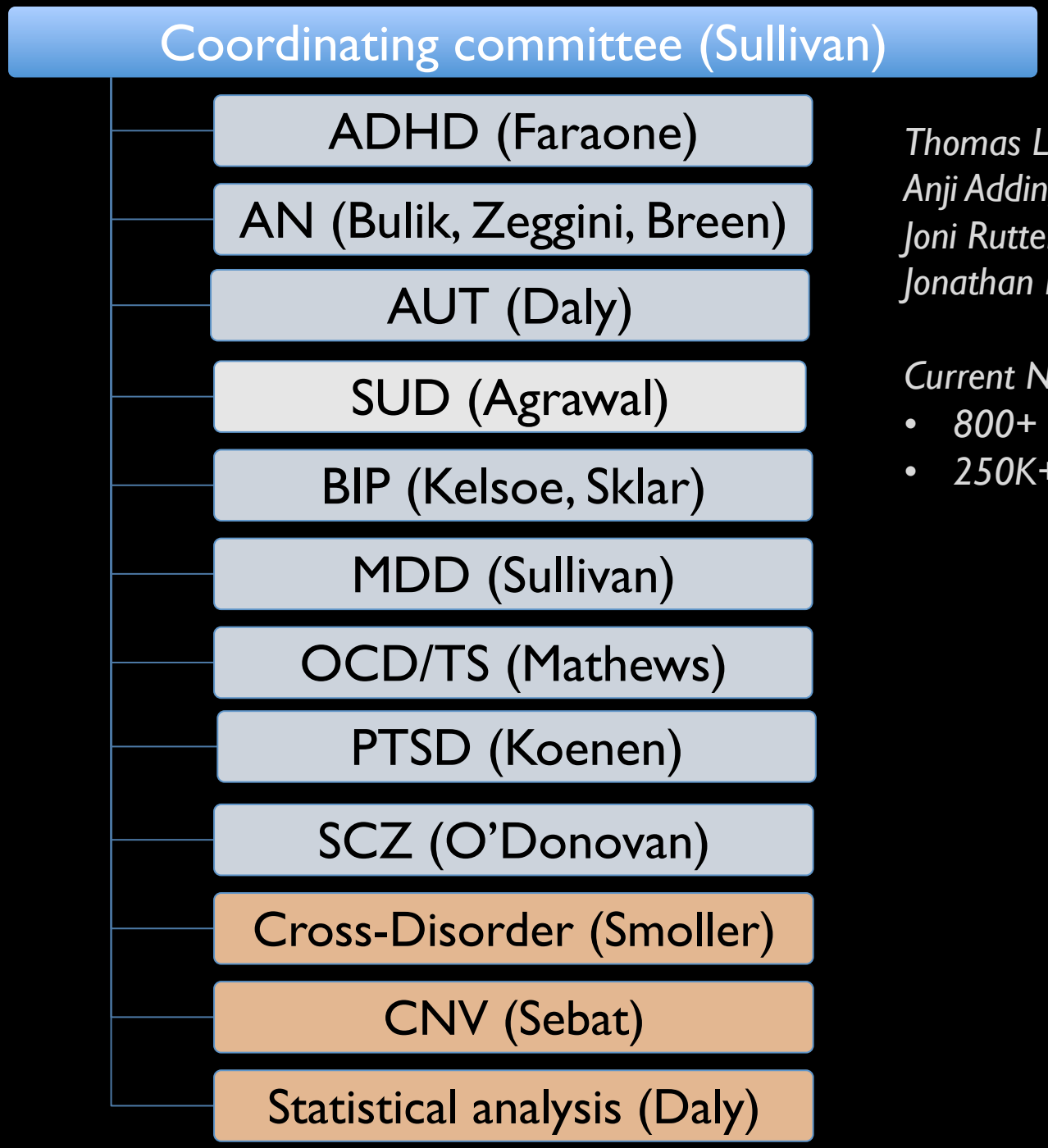
PGC history

Aim	PGC1	PGC2	PGC3
NIH funding	2009-11	2011-15	*6/5/2015*
NIH	NIMH	NIMH, NIDA	*NIMH, NIDA*
Philanthropy	–	yes *	*yes*
Data harmonization	yes	yes	*yes*
Number of cases	30K	264K	*546K*
Genotyping	no	yes	*no*
Aim: GWAS mega-analyses	5 disorders	9 disorders	*9 or 10*
Aim: cross-disorder	yes	yes	*yes*
Aim: CNV	no	yes	*yes*

5 disorders: ADHD, AUT, BIP, MDD, SCZ

9 disorders, plus: licit/illicit drugs, anorexia nervosa, OCD/TS, PTSD

* *Stanley Center, Mt Sinai, One Mind*



Thomas Lehner (NIMH)
Anji Addington (NIMH)
Joni Rutter (NIDA)
Jonathan Pollock (NIDA)

Current Ns:

- *800+ investigators*
- *250K+ subjects*

http://pgc.unc.edu

http://www.broadinstitute.org/mpg/ricopili

Psychiatric Genomics Consortium

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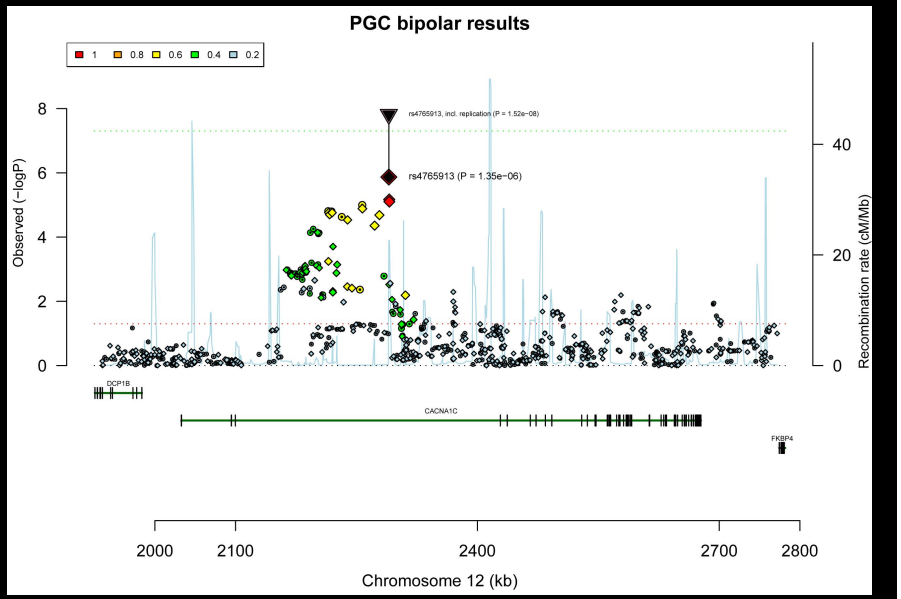
Downloads

Full results, all published papers



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Worldwide Lab Meeting

Meeting Documents

Click the link in the table below to download the PowerPoint slides for the indicated talk. If you missed a call and would like to hear what was discussed
column to the right of the Powerpoint slides. It's recommended that you download the matching PowerPoint Presentation to follow along.

Note: You can type http://pgc.unc.edu/worldwide to visit this page.

When playing call recordings on a mac, safari and chrome browsers are recommended.

Presenter	Date	PowerPoint Slides
Israel Liberzon	June 13 2014	Childhood Poverty and Emotional Regulation
Paul S. Appelbaum	May 9 2014	Informed Consent for Return of Incidental/Secondary Findings In Genomic Research
Ole A. Andreassen	Apr 11 2014	Boosting the Power of Psychiatric GWAS with New Statistical Tools
Peter Kraft	Mar 14 2014	Gene-Environment Interactions in Genome-Wide Association Studies: Conceptual and Statistical Issues
Kerry Ressler	Feb 14 2014	Post-Traumatic Stress Disorder: Understanding the Intersection of Gene, Environment, and Brain
Ronald Kessler	Jan 10 2014	The Global Burden of Mental Illness
John McGrath	Dec 13 2013	Where GWAS and Epidemiology Meet: Opportunities for the Simultaneous Study

Brain trust

- Many very smart people actively involved
- Major fraction of professional lives (for years now)
- Nearly all major groups
- Encompassing:
  - Clinical psychiatry/psychology/cog neuroscience
  - Brain imaging
  - Phenotype experts
  - Psychiatric genomics
  - Psychiatric epidemiology
  - Human genomics
  - Statistical genetics
  - Other "omics": gene regulation, eQTL, epigentics

Co-Funding

Figure 1. *Non-NIMH contributions to the PGC.*

PGC1 (9/08-8/10) & **PGC2** (5/11-3/16)

Stanley Center: co-funding for PsychChip

Stanley Center: analyst FTEs

One Mind for Research: PTSD analyst

VU Amsterdam: €1.2M free compute resources

Stanley Center: additional compute resources

Methods development from PIs

iPSYCH (DK): 80K new subjects (AUT, ADHD)

PGC3 (this proposal, 4/16-3/21)

NIDA: new funding for SUD in Aim 1

Science Foundation Ireland: new funding Aim 6

Stanley Center: new genotyping, analysts

AN: Klarman Family Foundation, Swedish Research Council, Charlotte's Helix Trust

SCZ European Union, UK MRC, Wales

New sample phenotyping, biobanking, genomic assays: multiple country-specific sources

NIMH 1:1 funding for PsychChip genotyping

Achievements

Area	Achievement
SNP mega-analyses	Significant associations: ADHD=1, AUT=1, MDD=1, BIP=19, SCZ=128
Papers	15 main [1-15], 27 secondary papers [16-42], 74+ others
New groups	AN, OCD/TS, PTSD, SUD
Psych Chip	PGC Psych Chip FAQ
Results freely available	PGC downloads
Worldwide lab talks	Slides & audio
Visualize results	Ricopili tool
PGC analyst training	Summer School (London June 22-26, 2015)

Figure 2. *PGC achievements.*

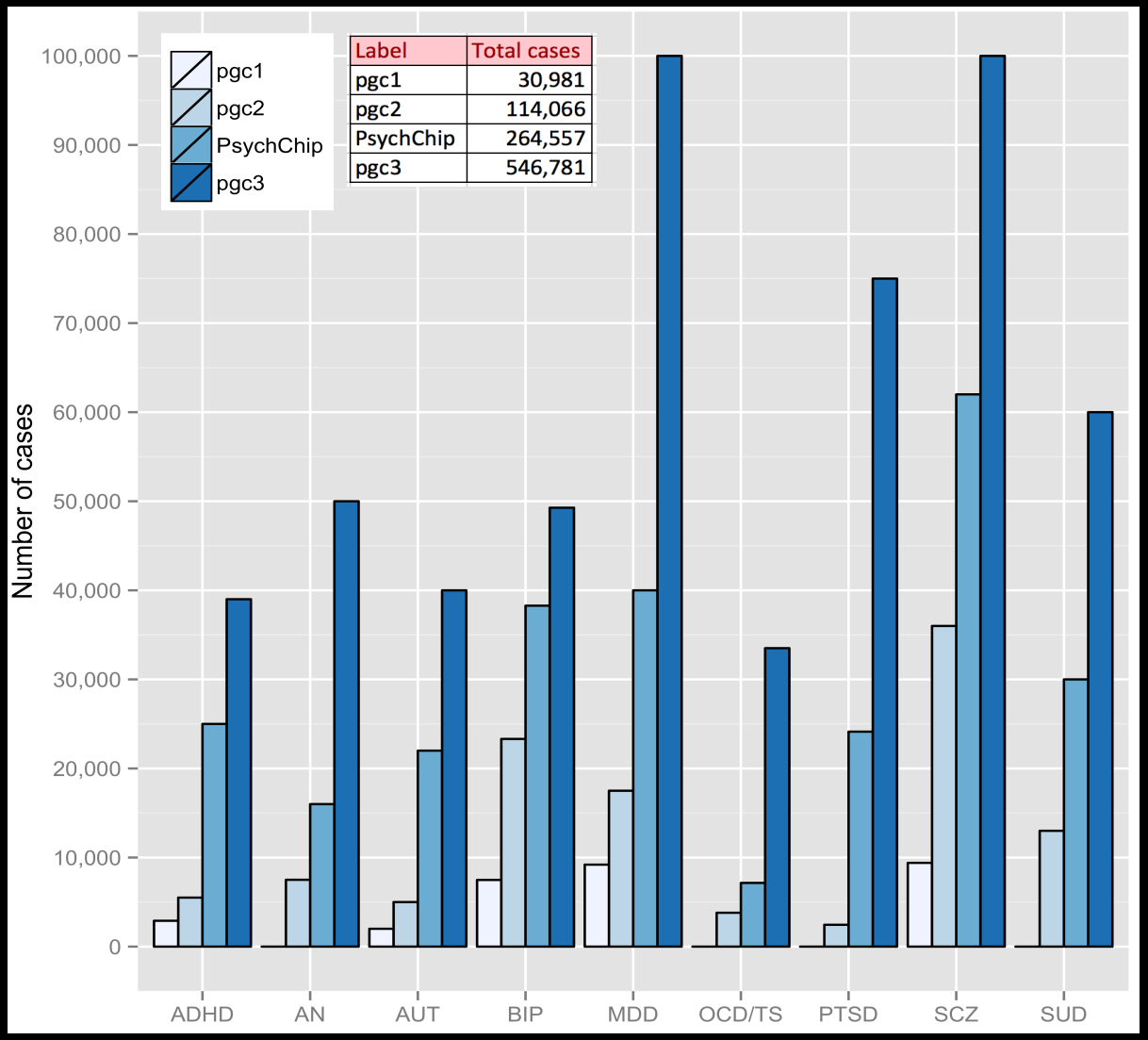


Figure 3. PGC N_{case} with GWAS. pgc1: initial PGC papers. pgc2: current N_{cases} (SCZ published, others in prep). pgc3: conservative N_{case} estimates for GWA available for analysis in Q1/2019.

PsychChip: purchased=150,247 arrays, completed=60.1%, ending date=Q3 2015

Group	Full methods	PGC3 N_{case}	Brief description
ADHD	[8] PMC	39K	**Diagnosis**: DSM-IV/ICD-10 ADHD, structured interviews, national treatment/pharmacy registers, or validated web instruments (new samples: iPSYCH, 23andMe). Includes PGC study quality review. **Ascertainment:** clinical or national register. **Phenotypes**: severity, symptoms, age onset, comorbidity.
AN		50K	**Diagnosis**: DSM-IV AN (excluding amenorrhea), structured interviews (new samples: ANGI & Charlotte's Helix). Includes PGC study quality review. **Ascertainment:** clinical or national register. **Phenotypes**: severity, symptoms, binging, purging, lowest/highest BMI, age onset, comorbidity.
AUT	[3] PMC	40K	
BIP	[12] PMC	49K	
MDD	[7] PMC	100K	**Diagnosis**: DSM-IV MDD, structured interviews, national treatment/pharmacy registers, or validated web instruments (new samples: iPSYCH & UK Biobank, Q1 2016). Includes PGC study quality review. **Ascertainment:** clinical or national register. **Phenotypes**: severity, symptoms, age onset, recurrence, comorbidity, sex abuse.
OCD/TS		34K	**Diagnosis**: DSM-IV OCD, structured interviews, national treatment registers, or validated web instruments (new samples iPSYCH & funded collections. Includes PGC study quality review. **Ascertainment:** clinical or national register. **Phenotypes**: severity, symptoms, age onset, comorbidity.
PTSD	[6] pending	75K	**Diagnosis**: DSM-IV PTSD, structured interviews, national treatment/pharmacy registers, or validated web instruments (new samples: DK Soldier). Includes PGC study quality review. **Ascertainment:** clinical, Army STARRS, or national register. **Controls** are trauma-exposed & separate from all other PGC groups. **Phenotypes**: traumatic event, severity, symptoms, age onset, comorbidity, trauma history.
SCZ	[1] PMC	100K	**Diagnosis**: DSM-IV SCZ or SAD, structured interviews or validate national treatment/pharmacy registers (new samples: CLOZUK v3, China, EUGEI). Includes PGC study quality review. **Ascertainment:** clinical or national register. **Phenotypes**: positive/negative symptoms, age onset, cognition, environmental exposures, brain MRI.
SUD	link	60K	**Diagnosis**: DSM-IV drug, tobacco, alcohol use disorders (new samples: "SmokeScreen", UK Biobank, other PGC). Includes PGC study quality review. **Ascertainment:** clinical or national register. **Phenotypes**: severity, quantity/frequency, symptoms, age onset, recurrence/relapse, craving, IV use, poly-drug.
Controls			

Figure xx. *PGC3 sample information. EXPLAIN abbreviations, Ncase (Q1 2019, gwas, confident, even conservative)*

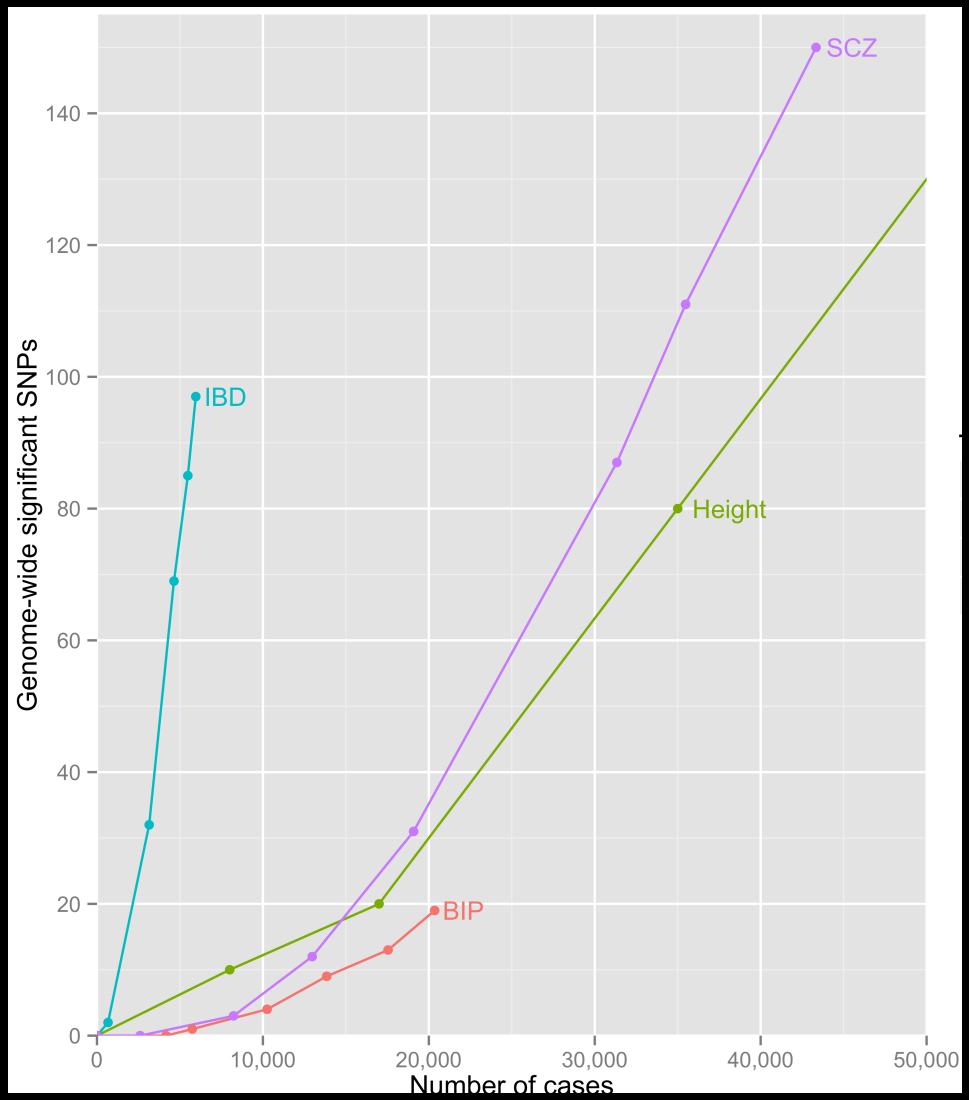


Figure 4. *N_{case} and genome-wide significant associations for SCZ and BIP in comparison to inflammatory bowel disease (IBD) and height ($N_{subjects}$). IBD has unusually favorable architecture; the others have lag phase followed by rapid growth.*

Aim 0 (unstated goals)

(a) Diversify. Sites: UNC, MGH, MSSM, UCSD + Cardiff, Dublin, WUSL

(b) Analysts & data wranglers funded by the PGC. Train others in Summer School

(c) Easier primary & secondary analyses: solve data access bottleneck

(d) Technical knowledge transfer

(e) PGC membership/author lists

(f) Do better with sample metadata

(g) Improve phenotype aggregation

Authorship

- Extremely important to PGC membership have updated authorship policies
- But, horrible procedurally
- Solution:
  - ORCID http://orcid.org
  - PIs are in charge of authorship for their study
  - Investigators control their details
  - NB: we will have authorship freezes
- Makes it practical to have 100s of authors

Common

Aim 1

SNPs.

(a) Enlarge GWAS mega-analyses to increase understanding of disorders for which major progress has been made and to accelerate new discoveries

(b) Systematic cross-disorder analyses

(c) Pathway analyses. Include academic and industry experts in psychopharmacology to maximize therapeutic implications of the findings

Common

Shadow Aim 1

- *Increase genotyped Ns for 9 disorders to 100K cases*

- *Not as bad as it sounds:*
  - *Likely: MDD, SCZ, smoking*
  - *PGC should soon have 400K, need 600K more*

- *Requires:*
  - *Genotype existing samples!*
  - *Innovation*
  - *Social media*
  - *Funding: EU sources, philanthropy, NIH, pharma*

Common

Clarification

- Rapid phenotyping acceptable: if & only if there is a rigorous validation study

- E.g., Sweden SCZ Study (≥2 SCZ/SAD admits)
  - Medical record review
  - Pop prev, recurrence risks, h^2, r_g SCZ-BIP
  - Genotype h^2 & r_g (note utility of ldsc)
  - → all consistent

Common

Aim 2

Genetic risk scores (GRS).

(a) Development: using existing data from large longitudinal cohorts, evaluate the pleomorphic effects of GRS over developmental time

(b) Extremes: analyze phenotype data from cases with very high or very low GRS to understand the clinical impact of genetic burden

(c) Cross-disorder: develop a general GRS for psychopathology to evaluate risk and resilience across PGC disorders (includes NIMH RDoC)

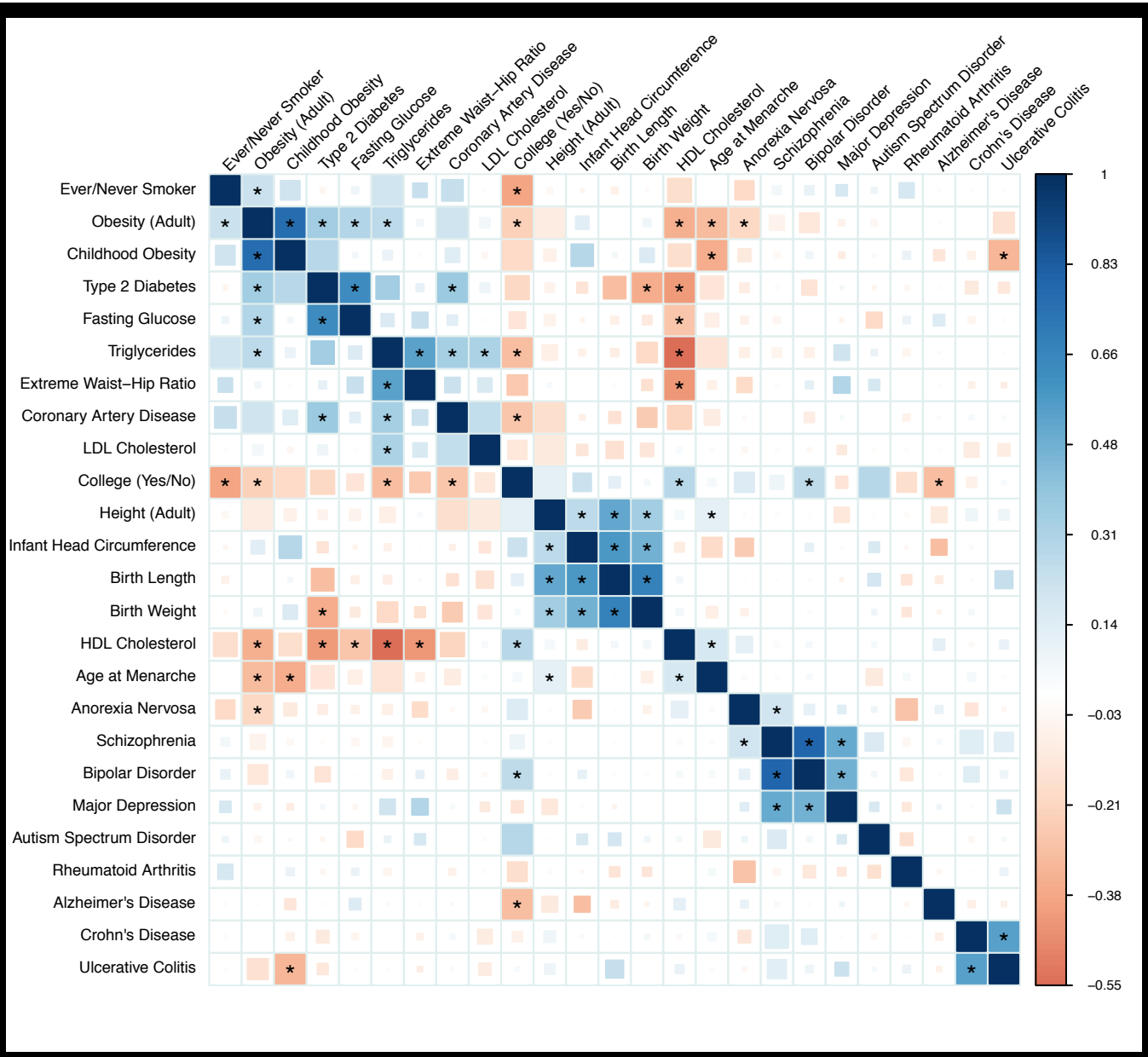
Common

Aim 3

Brainstorm.

Apply novel statistical methods to GWAS results to estimate pairwise genetic correlations among all PGC disorders and all obtainable CNS-relevant diseases/ quantitative traits (e.g., epilepsy, MRI, personality, IQ) to develop a comprehensive view of genetic influences across a broad set of brain phenotypes.

Common



Background (also PGC Stat Gen talk last week):

http://www.ncbi.nlm.nih.gov/pubmed/25642630

http://biorxiv.org/content/early/2015/01/27/014498

Rare

Aim 4

CNV.

Analyze rare CNVs in nine psychiatric disorders via high-quality mega-analyses, and perform cross-disorder analyses to reveal pleiotropic genetic effects.

Rare

Aim 5

Sequencing.

Characterize the full spectrum of genetic variation (especially rare variants of strong effect) in regions implicated by PGC GWAS. Inexpensively sequence coding and regulatory regions of ~200 candidate genes in 20,000 independent subjects.

Rare

Aim 6

Pedigree sequencing.

The large network of PGC clinicians have identified rare, densely affected pedigrees. Using whole genome sequencing (30x coverage), we will systematically evaluate ~100 such pedigrees to enable searches for rare variants of strong effect.

(1:1 co-funding via Science Foundation Ireland)

Rare

Aim 6 – Gill & Corvin, Dublin

- Hundreds of clinicians in the PGC
- Have taken family histories for very large numbers of patients
- Across the PGC:
  - Find best 100 unusual pedigrees (large, dense, odd, comorbid, etc)
  - PGC pays for genomic assays and analysis
  - Collaborate on writing the paper

- *"to my knowledge, no compelling Mendelians for SCZ"*
- *There are a few for AUT and ALZ*
- *Rigorous test – can we find any?? Even one?*

What's the logic?

Psych drug discovery – serendipity (!)

Genetic findings

↓

Biology

↓

Pathways / "read outs"

↓

Rational drug discovery

Convergence

Box 1. Summary of genomic findings for schizophrenia.

Genomic class	Findings	Comments
Gene sets	Neuronal calcium signaling [4,19] Post-synaptic density ARC complex [4,5,25] NMDA receptor [4,5,25] FMRP interactors [4,19]	Convergent evidence from exome, CNV, and/or common variant studies. Often includes both existing variation in case-control samples as well as *de novo* variation.

Progress since WCPG 10/2014

- PGC Analyst Training Summer School
  - London, June 22nd-26th 2015
  - 24 slots for experienced analysts
  - cathryn.lewis@kcl.ac.uk or gerome.breen@kcl.ac.uk
- New analyst, with Stephan Ripke in Berlin

Thanks: Stanley Center, Cathryn, Gerome, teaching staff

Discussion !