Beginning the PGC3 grant

Patrick Sullivan ***for the PGC***

University of North Carolina / Karolinska Institutet

PGC (briefly)

PGC overview

- *2007-present*
- *9 disorders*
- *900+ scientists in PGC, largest consortium ever*
- *Results freely available*
- *Papers: 17 main, 31 secondary/methods, 75+ use our results*
- *Many highly cited or "hot" papers*

PGC3 grant, 6/2016 – 4/2021

SUMMARY STATEMENT
(Privileged Communication)

PROGRAM CONTACT:
Geetha Senthil
301-402-0754.
geetha.senthil2@nih.gov

Release Date: **11/24/2015**

Application Number: **1 R01 MH109528-01**

Principal Investigator

SULLIVAN, PATRICK F MD

Project Title: **1/7 Psychiatric Genomics Consortium: Finding actionable variation**

SRG Action: **Impact Score: 13** **Percentile: 1 #**

RESUME AND SUMMARY OF DISCUSSION: This collaborative application from seven sites proposes development of the next phase of the Psychiatric Genetics Consortium (PGC). The PGC has had an exceptional impact on the field of psychiatric genetics and the proposed analysis phase promises even further important discoveries. The scientific team is a stellar group of investigators with the qualifications to achieve further superlative results. Overall the approach is comprehensive and sweeping in scope with negligible concerns. The panel was very enthusiastic and all agreed that the study is likely to have an exceptionally high impact on the field of psychiatric disorders.

PGC history

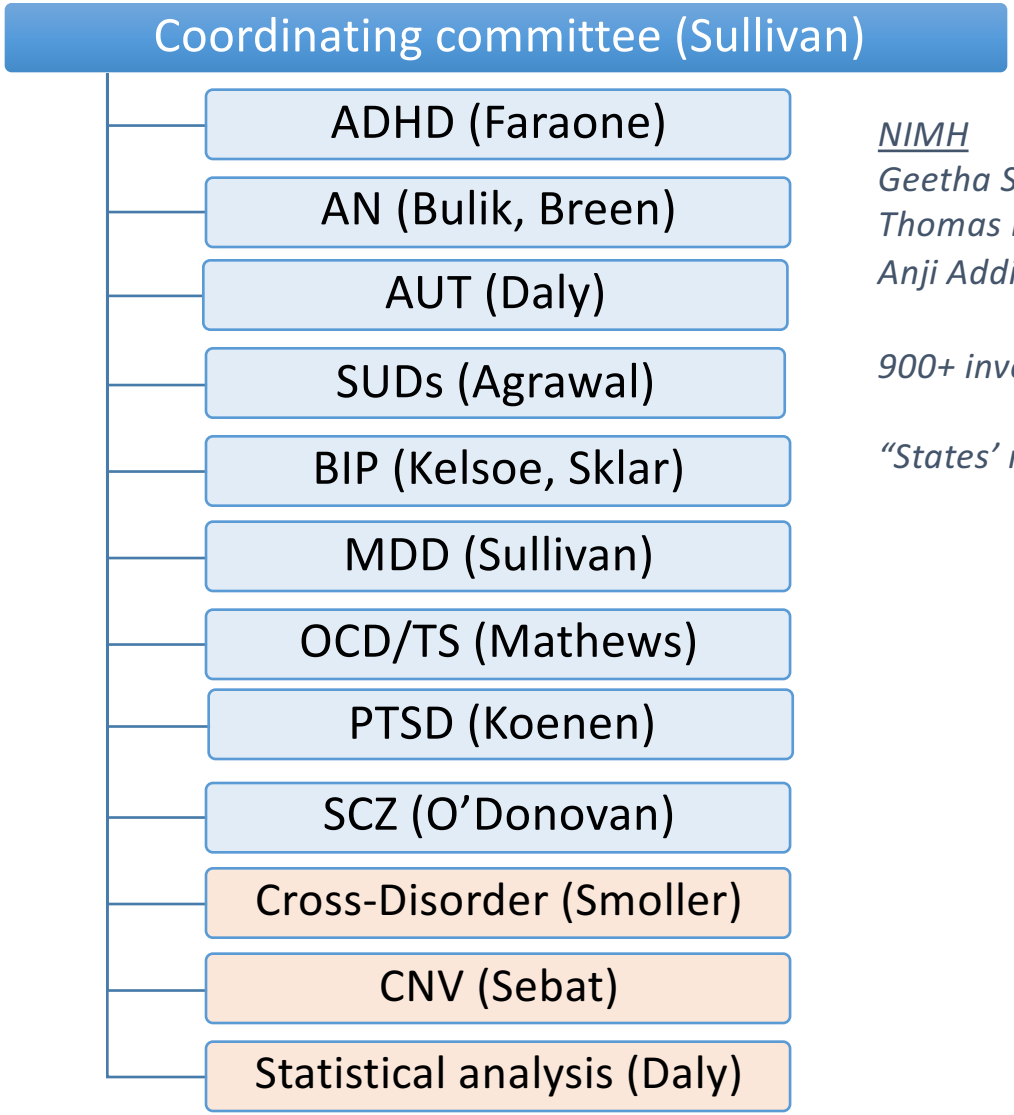
Aim	PGC1	PGC2	PGC3
NIH funding	2009-11	2011-16	*2016-2021*
NIH	NIMH	NIMH	*NIMH, NIDA*
Co-funding	–	yes *	*yes* * ‡
Data harmonization	yes	yes	*yes*
Number of cases	30K	264K	*600K+*
Aim: GWAS mega-analyses	5 disorders	9 disorders	*9 disorders*

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

9 disorders: add eating disorder, OCD/TS, PTSD, SUDs

Funders

Science Foundation Ireland & Norwegian Research Council



NIMH
Geetha Senthil
Thomas Lehner
Anji Addington

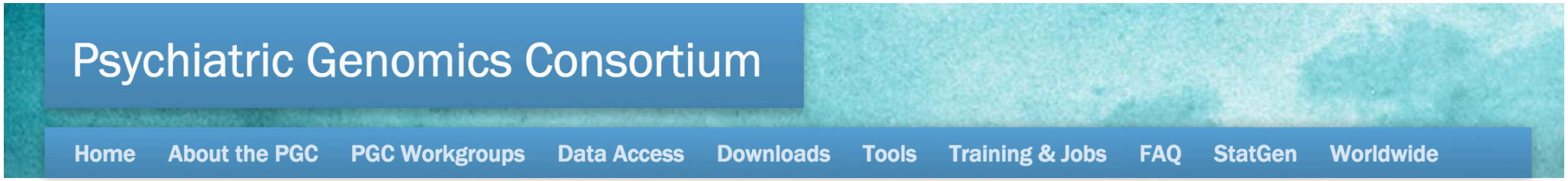
900+ investigators

"States' rights model"

“Growing pains” fixes

In 2009, no one thought the PGC would be around in 2020 …

Updated web page

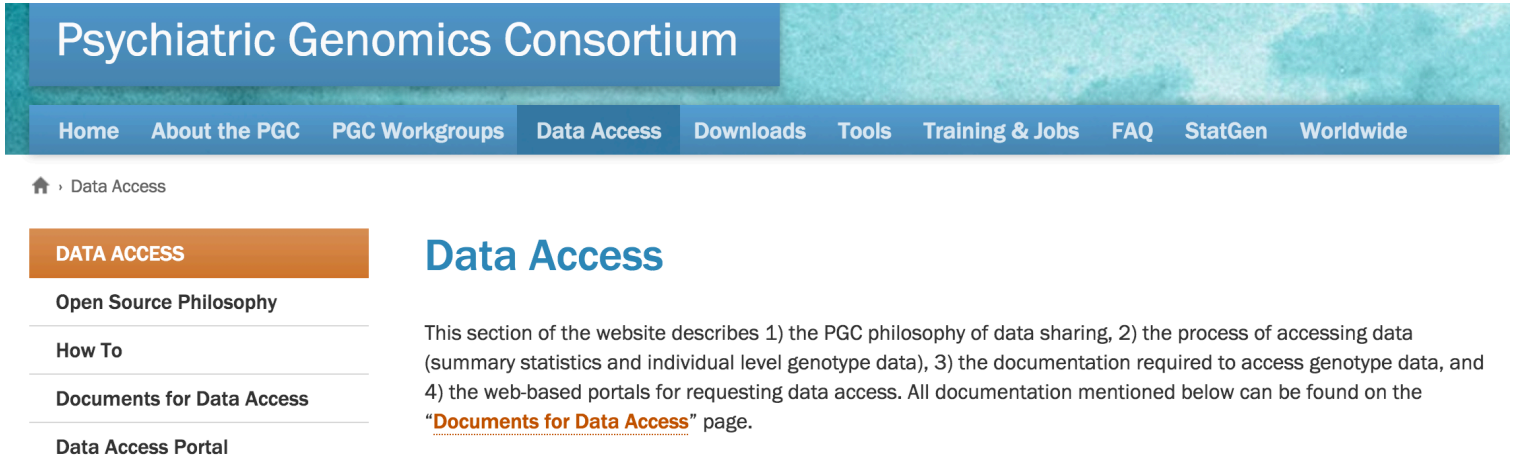


Thanks 1e6 to: Krista Latta, Lea Davis, Gerome Breen, Cindy Bulik, Michael Gill

Great sections all around

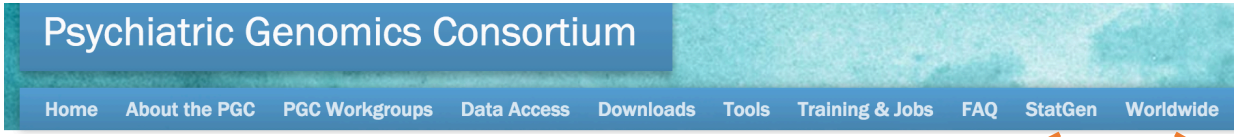
In particular, the extensive FAQ & newbie sections

Data Access Committee



Lea Davis for the Data Access Committee	July 8 2016	**Data Access Demystified: A complete guide to obtaining genotype data for PGC members**	0:00

PGC talks



Presenter	Date	Slide Presentation PDF	Call Recordings
Sarah Medland	June 28 2016	Methodological Issues in Imaging Genetics	00:00 / 58:55
Michael Neale	Apr 26 2016	Pitfalls in GxE Research and How to Avoid Them	Audio Not Available
Daniel Howrigan	Mar 22 2016	PGC CNV analysis: Data management and analysis considerations for consortium level data	00:00 / 63:48
Christiaan de Leeuw	Feb 23 2016	The statistical properties of gene-set analysis	00:00 / 57:56
Hilary Finucane	Jan 26 2016	Heritability enrichment of differentially expressed genes in psychiatric traits	00:00 / 56:28
Jonathan Mill	June 10 2016	Integrating genetic and epigenetic variation in schizophrenia	00:00 / 57:34
Pamela Sklar	May 13 2016	The CommonMind Project: Generating and integrating biological data to interpret genetics	00:00 / 60:21
Jeremiah Scharf (OCD/TS), **Caroline Nievergelt** (PTSD), **Stephan Ripke** (SCZ), and **Raymond Walters** (SUD)	Apr 8 2016	Past, current, and future work of the workgroups	Please see PGC group listservs for audio and slide set.
Raymond Walters (ADHD), **Richard Anney** (AUT), **Eli Stahl** (BIP), and **Gerome Breen** (MDD)	Mar 11 2016	Past, current, and future work of the workgroups	Please see PGC group listservs for audio and slide set.
Manolis Dermitzakis	Feb 12 2016	The Genotype-Tissue Expression (GTEx) pilot analysis: multi-tissue gene regulation in humans	00:00 / 56:05
Jonathan Sebat	Jan 8 2016	Large scale studies of CNV across the major psychiatric disorders	00:00 / 58:32

Shift to dissemination of methods

Ricopili training

Ricopili is the PGC gwas pipeline, https://github.com/Nealelab/ricopili

There have been 2 training sessions in London (June 2015 & 2016)

Trained 24 & 45 analysts.

https://sites.google.com/a/broadinstitute.org/pgc-summer-school-2016

Hope to repeat in 2017

Thanks to Cathryn Lewis & Gerome Breen (IOPPN organizers)

Stanley Center for major funding

Communications

UNC listservs for most groups

Multiple Google Groups

Key google group is this one (N=968)
https://groups.google.com/forum/?hl=en-GB#!forum/pgc-full-consortium

Point person = Krista Lattl· (UNC)

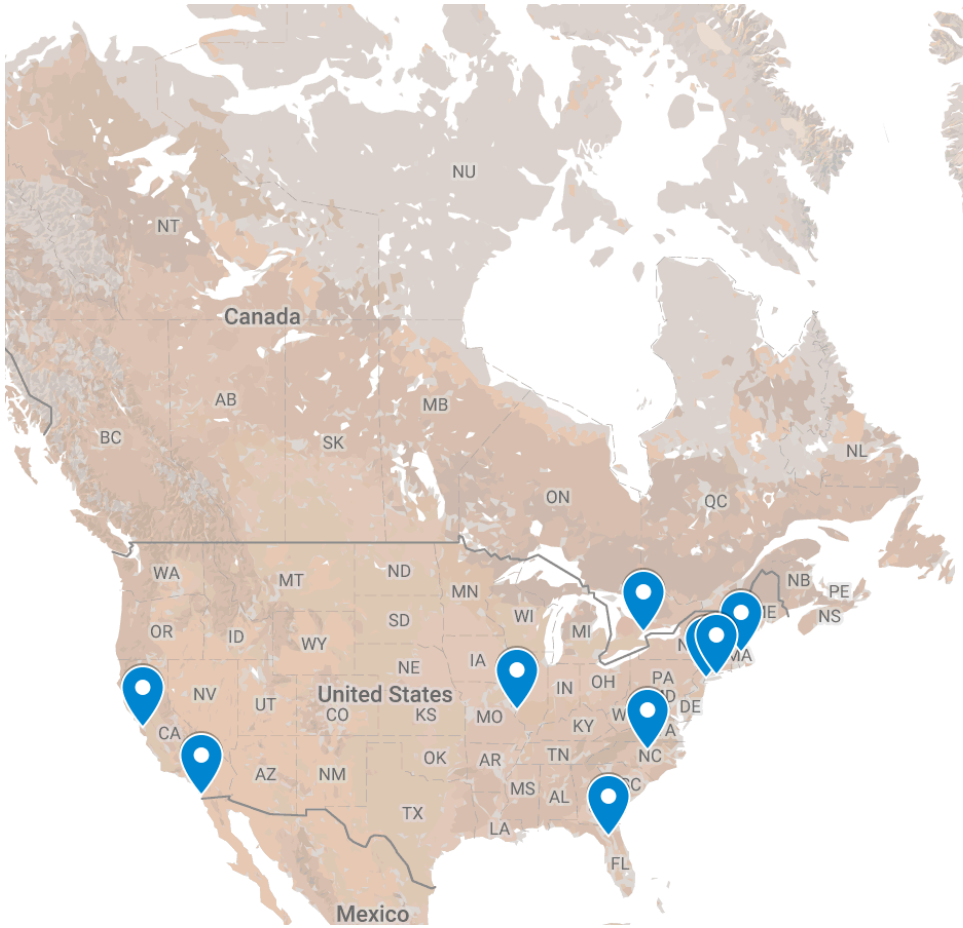
Bioinformatics

Building bioinformatics tools on LISA to understand output

- Basic annotations (genes, GWAS catalog, OMIM, psych CNVs, ID/ASD)
- Making a ”gene matrix” (using R, extensible, modifiable)
- Genetic correlations & lookup vs all PGC results
- Make input data for LD-Hub
- MAGMA pathway analysis; TWAS; causal SNP identification; partitioned LDSC; etc

Doing pilot project with psychENCODE to add functional genomic data

PGC3 grant



Country	Authors
CA	10
DK	10
ES	14
AU	16
CH	17
NO	17
SE	17
NL	35
GB	39
DE	58
US	127

and Brisbane Australia

ORCID lists ADHD, AN, BIP MDD OCD/TS SUD

Structure

Site	Site lead	Note	1	2	3	4	5	6
Cardiff	O'Donovan, Mick	Largest site	✓					
Dublin	Gill, Michael	Big peds						✓
Mass Gen Hosp	Daly, Mark	gma/brainstorm	✓ ✓		✓			
Mt Sinai	Sklar, Pamela	Targeted seq					✓	
UCSD	Sebat, Jonathan	CNV				✓		
UNC	Sullivan, Patrick	Coordination		✓				
Wash U St Louis	Agrawal, Arpana	SUDs - NIDA	✓					

Overall, 65% of budget → 9 analysts + 5 data wranglers + core admin staff

The PGC is hiring!

"Finding actionable variation"

Goal is to deliver actionable findings, genomic results that

a) reveal the fundamental biology,
b) inform clinical practice, and
c) deliver new therapeutic targets

This is the central idea of the PGC: to convert genetic risk factors into biologically, clinically, and therapeutically meaningful insights.

Aim 1 (core business)

Common

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 – paper in press in Nature Neuroscience

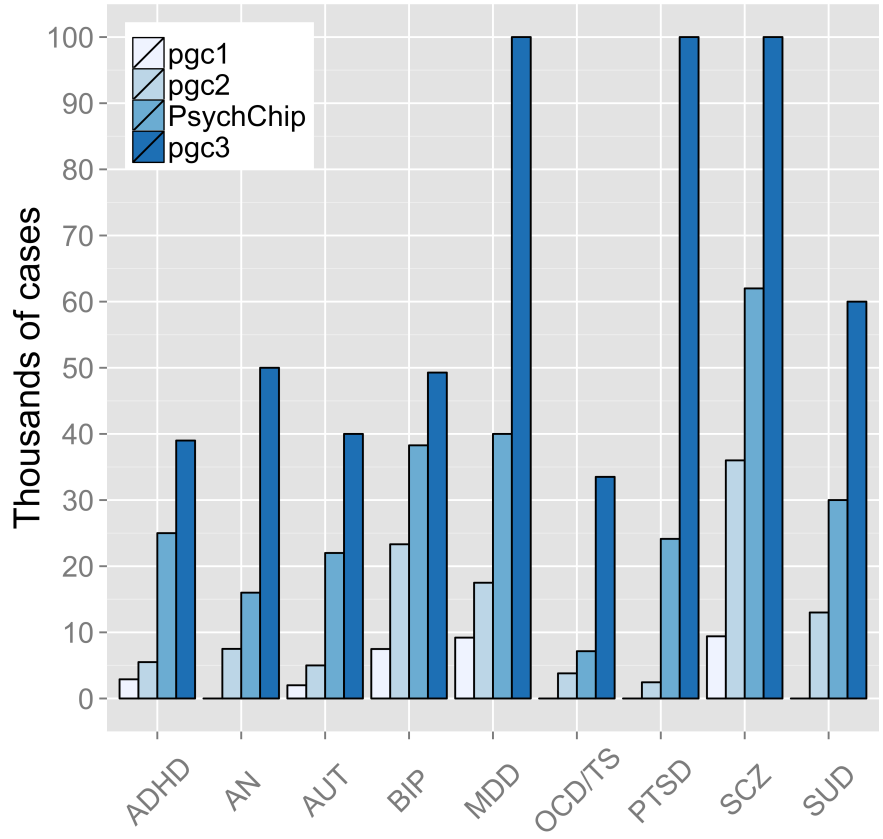
Goal – 100K cases for each disorder

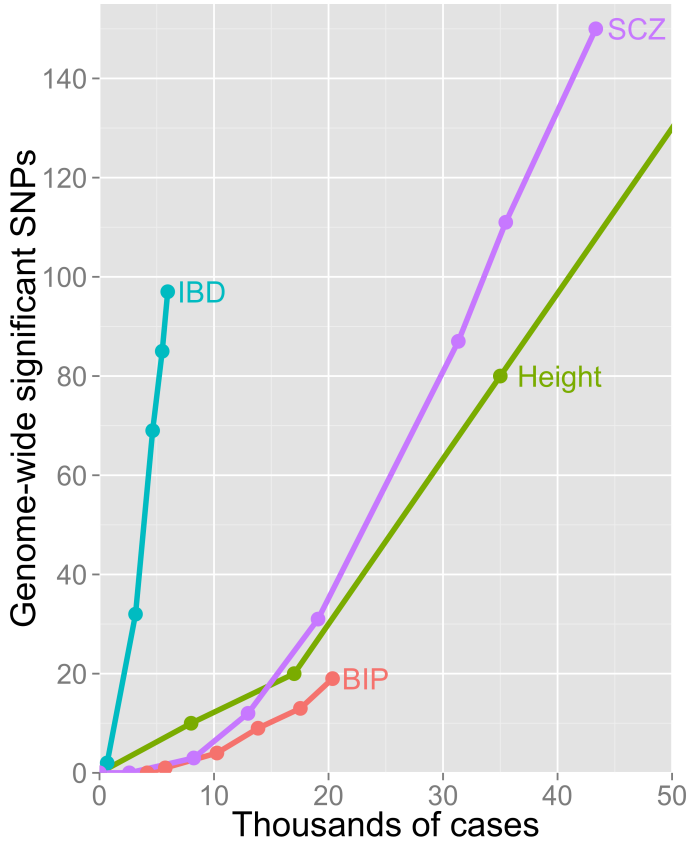
In preparation (data in PGC or soon)

Disorder	New loci
SCZ - CLOZUK	*50*
BIP	*12*
MDD	*9*
ADHD - *i*PSYCH	*9*
AUT - *i*PSYCH	*5*
AN	*1*
SUDs	*1*

Fingers crossed for OCD/TS & PTSD

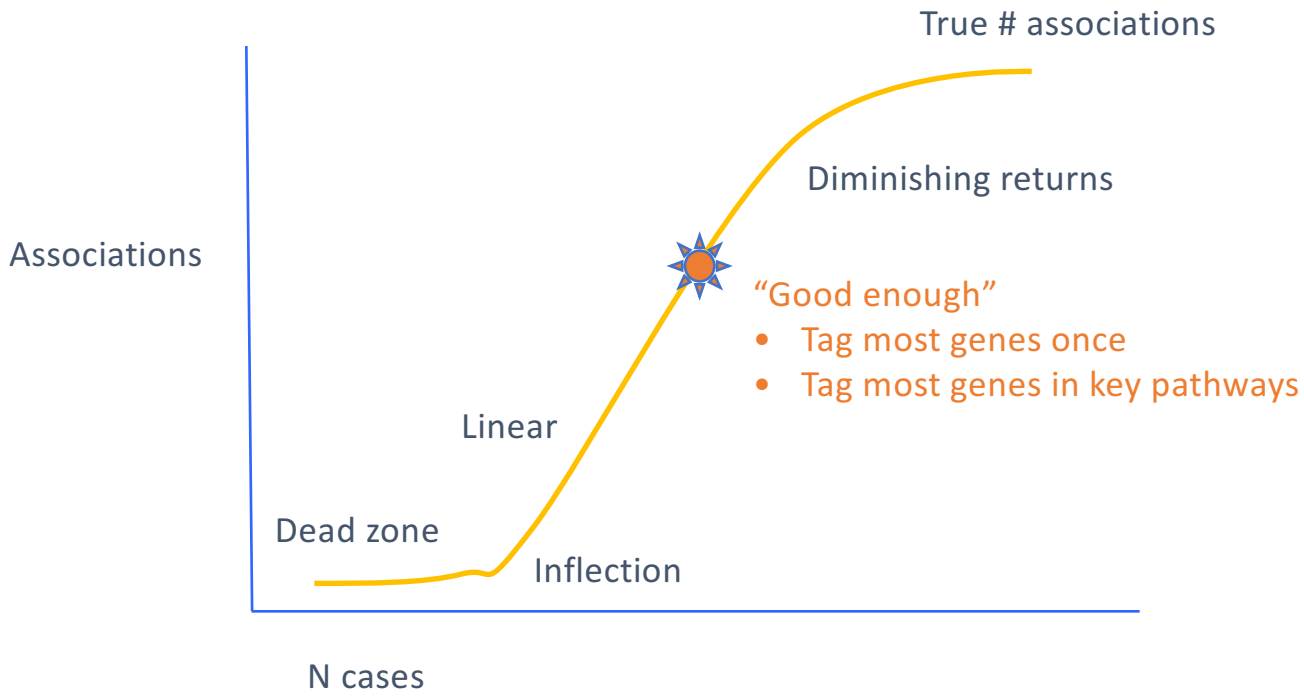
PGC3 sample sizes





N_{case} with GWAS. pgc1: initial PGC papers. pgc2: current N_{cases} . pgc3: conservative N_{case} estimates for Q1/2019

What's the end point?



Aim 2

Common

<u>Genetic risk scores (GRS)</u>

(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 RDoC)

Aim 2 – need to form working group

Intention is to form a working group of studies with:

- *Longitudinal cohort studies*
- *2+ measurement points*
- *Multiple psychiatric phenotypes (disorder and/or symptom scales*
- *Have GWAS now & sharable with PGC*

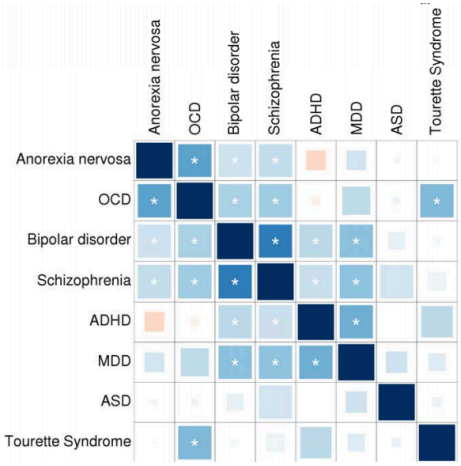
Email Krista please if you want to hear more

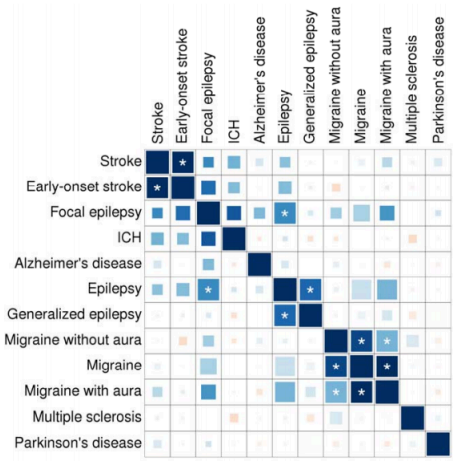
Aim 3

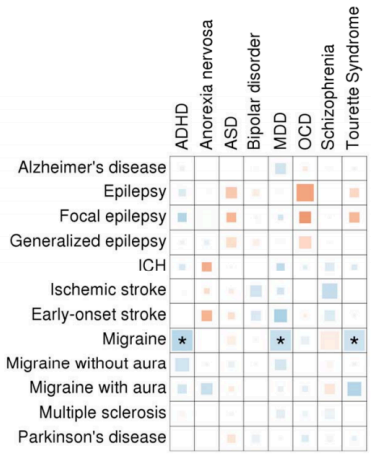
Common

Brainstorm

Estimate genetic correlations among all PGC disorders and all CNS-relevant diseases/quantitative traits to develop a comprehensive view of genetic influences across a broad set of brain phenotypes.







http://biorxiv.org/content/early/2016/04/16/048991

Aim 4

Rare

CNV

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

We need to get intensity files uploaded to LISA

This is being coordinated by CNV group (J Sebat) & working groups

Aim 5

Rare

<u>Sequencing</u>

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.

Aim 6

Rare

<u>Pedigree sequencing (co-funded by Science Foundation Ireland)</u>

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.

“PGC3: finding actionable variation”

Actionable

Goal is to deliver actionable findings, genomic results that

a) reveal the fundamental biology,
b) inform clinical practice, and
c) deliver new therapeutic targets

This is the central idea of the PGC: to convert genetic risk factors into biologically, clinically, and therapeutically meaningful insights.

What's the logic?

Genetic findings

↓

Biology

↓

Pathways / "read outs"

↓

Rational drug discovery / clinical use

Actionable – rare variant aims

Aim	biol / clin / ther			Comment
Rare – 6 – large pedigrees	✓		✓	A big swing for the fence – even 1 would be notable
Rare – 5 – targeted sequencing	✓		✓	Can any genes get over the exome sig threshold?
Rare – 4 – CNVs	✓	✓	✓	Especially single gene CNVs (e.g., *NRXN1* & *C4* CNP)
Common – 3 – brainstorm				
Common – 2 – GRS over dev				
Common – 1 – core business, gwas				

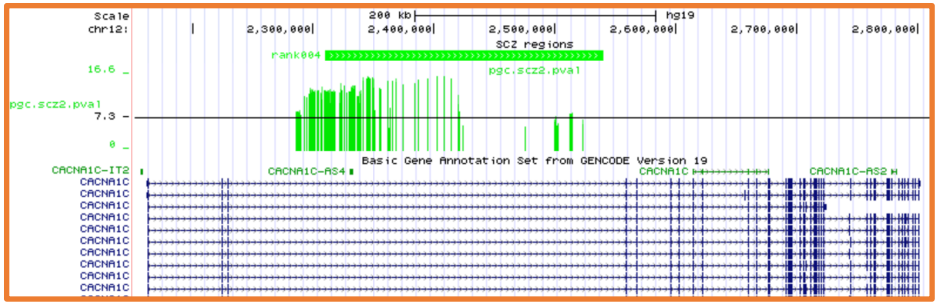
Easy to connect a genetic finding to a specific gene with hypothesis of mechanism

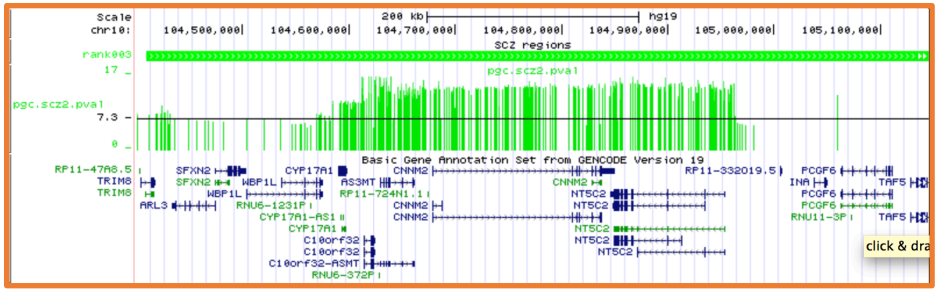
Actionable – common variant aims

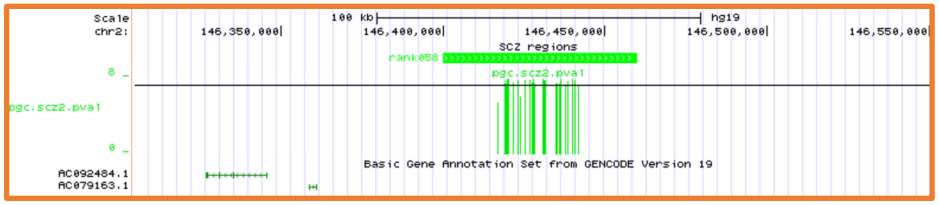
Aim	biol / clin / ther			Comment
Rare – 6 – large pedigrees	✓		✓	A big swing for the fence – even 1 would be notable
Rare – 5 – targeted sequencing	✓		✓	Can any exons get over the RV threshold?
Rare – 4 – CNVs	✓	✓	✓	Especially single gene CNVs (e.g., *NRXN1* & *C4* CNP)
Common – 3 – brainstorm		✓		Nosology
Common – 2 – GRS over dev		✓		Etiology, GxE, gen epi
Common – 1 – core business, gwas	✓	✓	✓	Bread-and-butter of the PGC

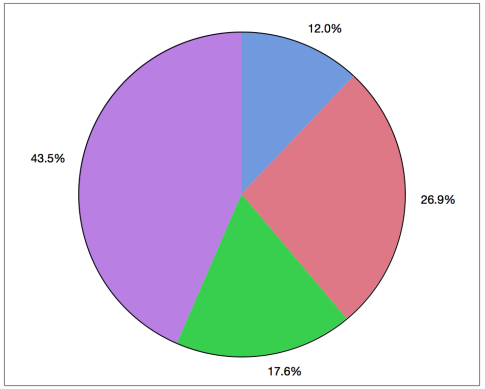
Connection of findings to genes requires multiple assumptions

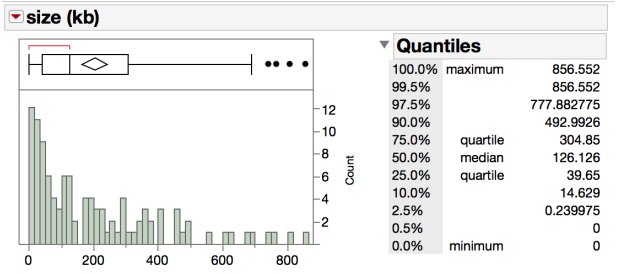
How to connect common variants to genes?











The PsychENCODE project

The PsychENCODE Consortium*, Schahram Akbarian, Chunyu Liu, James A Knowles, Flora M Vaccarino, Peggy J Farnham, Gregory E Crawford, Andrew E Jaffe, Dalila Pinto, Stella Dracheva, Daniel H Geschwind, Jonathan Mill, Angus C Nairn, Alexej Abyzov, Sirisha Pochareddy, Shyam Prabhakar, Sherman Weissman, Patrick F Sullivan, Matthew W State, Zhiping Weng, Mette A Peters, Kevin P White, Mark B Gerstein, Geetha Senthil, Thomas Lehner, Pamela Sklar & Nenad Sestan

exactly →

Recent research on disparate psychiatric disorders has implicated rare variants in genes involved in global gene regulation and chromatin modification, as well as many common variants located primarily in regulatory regions of the genome. Understanding precisely how these variants contribute to disease will require a deeper appreciation for the mechanisms of gene regulation in the developing and adult human brain. The PsychENCODE project aims to produce a public resource of multidimensional genomic data using tissue- and cell type–specific samples from approximately 1,000 phenotypically well-characterized, high-quality healthy and disease-affected human post-mortem brains, as well as functionally characterize disease-associated regulatory elements and variants in model systems. We are beginning with a focus on autism spectrum disorder, bipolar disorder and schizophrenia, and expect that this knowledge will apply to a wide variety of psychiatric disorders. This paper outlines the motivation and design of PsychENCODE.

How can I get involved with the PGC?

This is do-able

Much of PGC leadership is 55+. Turnover is good for an organization.

The people who are in leadership roles in PGC stepped up:

- Volunteered, followed through, did tasks well
- Took on small roles, did them well, got more to do
- Volunteered to write parts of papers
- Were consistently on calls

PGC FAQ

7. I am a part of the PGC already, how do I get more involved?

Fantastic question, there is always more to do and we always need more help! The best first step is to talk with your **working group chair** to see what needs to be done. Since we are a voluntary organization, people often get involved by volunteering to do sometimes inelegant and low level tasks. The PGC is a labor of love and we welcome enthusiastic and dedicated workers. We live by the rules of sweat equity and you are rewarded for the effort you dedicate to the consortium. We anticipate turnover of PGC leadership over the next several years, so getting involved now will position you well for the future.

N=418 who've done ORCID: Abdellaoui, Adkins, Adolfsson, Agartz, Agrawal, Air, Akil, Alda, Alliey-Rodriguez, Andlauer, Andreassen, Anjorin, Arnold, Arranz, Aschauer, Bacanu, Baker, Banaschewski, Barchas, Barta, Bass, Bau, Bauer, Baune, Beekman, Bergen, Berger, Bethell, Bienvenu, Biernacka, Bierut, Bigdeli, Blackwood, Boden, Boehnke, Boks, Boomsma, Boraska Perica, Børglum, Breen, Brown, Bulik, Bunney, Burmeister, Buttenschøn, Byrne, Cappi, Carracedo, Casas Bruguã, Casas Brugué, Castelao, Cath, Cervantes, Chen, Chou, Cichon, Clarke, Collier, Cook, Copeland, Corley, Cormand, Costello, Courtet, Couvy-Duchesne, Craddock, Crowley, Cruceanu, Cullen, Culverhouse, Curtis, Czerski, Dale, Dalsgaard, Dalvie, Dannlowski, Davis, De Geus, Degenhardt, Del Favero, Delorme, Dempfle, Denys, Depienne, Derks, Derringer, Di Florio, Direk, Djurovic, Dmitrzak-Weglarz, Domenici, Doyle, Duncan, Dunn, Eapen, Edenberg, Ehrlich, Elvsåshagen, Esko, Fan, Farrer, Favaro, Fernandez, Fernandez-Aranda, Figee, Fischer, Flickinger, Forstner, Forty, Frank, Fraser, Freimer, Frye, Fullerton, Gaddis, Gelernter, Geller, Gershon, Giegling, Gilbert, Gill, Goes, Gonidakis, Gordon, Gordon-Smith, Grabe, Grados, Green, Greenberg, Grevet, Grice, Grigoroiu-Serbanescu, Grove, Grünblatt, Guan, Guijarro, Guillaume, Guzman-Parra, Haavik, Hack, Hakonarson, Hamilton, Hammerschlag, Hamshere, Hancock, Hanna, Hansen, Hartmann, Hartz, Hatzikotoulas, Hauser, Hautzinger, Hayward, Heath, Heiman, Henders, Herms, Herpertz-Dahlmann, Hervas, Hewitt, Hickie, Hinney, Hoekstra, Hoffmann, Hofman, Hohmann, Holmans, Homuth, Hopfer, Horn, Horwood, Hottenga, Hultman, Hutz, Ibanez, Ising, Jankovic, Jansen, Jimenez-Murcia, Johansson, Johnson, Jones, Juréus, Kandaswamy, Kaprio, Karlsson, Kendler, Kennedy, Kent, Kiefer, King, Kirov, Kittel-Schneider, Kloiber, Klump, Knott, Knowles, Knudsen, K[illegible]n, [illegible], Konte, Kral, Krauter, Krogh, Kuntsi, Kupka, Kutalik, Landén, Lang, Langley, Lawrence, Leber, Lesch, Levinson, Levy, Lewis, Li, Lichtenstein, Lissowska, Liu, Loo, Lucae, Lynskey, Maaser, Macintyre, Madden, Maes, Magnusson, Maher, Malt, Martin, Mathews, Mattheisen, Mayoral-Cleries, Mcelroy, Mcgough, Mcgrath, Mcguffin, Mcintosh, Mckay, Mclaughlin, Mcqueen, Mcquillin, Medland, Mehta, Melle, Meng, Metspalu, Micali, Middeldorp, Mihailov, Milaneschi, Milani, Mitchell, Moessner, Monteleone, Montgomery, Morken, Mors, Mota, Mühleisen, Müller-Myhsok, Müller-Vahl, Munn-Chernoff, Myers, Nagy, Nauck, Nelson, Nestadt, Nicolini, Nigg, Nöthen, Nurmi, Nurnberger, Nyholt, O'donovan, Oedegaard, Olde Loohuis, Onnink, Ophoff, Ori, Oruc, Owen, Paciga, Pálmason, Papeå¾Ovã¡, Paschou, Pauls, Pearson, Pedersen, Penninx, Pergadia, Perlis, Perry, Peterson, Pettersson, Peyrot, Pfennig, Piras, Polderman, Porteous, Posthuma, Potash, Preisig, Quiroz, Ramos-Quiroga, Rasmussen, Regeer, Reichborn-Kjennerud, Reif, Reinbold, Rhee, Ribases, Rice, Richter, Ridinger, Rietschel, Riley, Ripke, Rivas, Rivera, Rizzo, Rommelse, Rothenberger, Rouleau, Rujescu, Sã Nchez-Mora, Saccone, Saeed Mirza, Samuels, Sànchez-Mora, Sandor, Scherag, Scherbaum, Schimmelmann, Schlögelhofer, Schoevers, Schofield, Schulze, Scott, Shi, Sinnamon, Sinzig, Slof-Op 'T Landt, Smalley, Smit, Smoller, Sonuga-Barke, Soyka, Spalletta, Spijker, Stallings, Steffens, Stein, Stordal, Strauss, Streit, Strohmaier, Stuhrmann, Sullivan, Szatkiewicz, Tansey, Tarnok, Tarter, Teumer, Thapar, Thompson, Thornton, Tiemeier, Tischfield, Todorov, Treutlein, Turecki, Uher, Uhlmann, Uitterlinden, Umbricht, Vaaler, Van Den Heuvel, Van Der Auwera, Van Furth, Van Grootheest, Van Hemert, Vanyukov, Viktorin, Vincent, Völzke, Vulink, Walitza, Wall, Walters, Wang, Wang, Watson, Webb, Weissman, Wellmann, Werge, Willemsen, Wilmot, Winslow, Witt, Wodarz. Worbe. Wrav. Xi. Xu. Yanovski. Yao. Yilmaz. Yu. Zai. Zavats. Zeaaini. Zerwas. Zill

THANKS