PGC Worldwide Lab Call Details

DATE: Friday, June 12th, 2015

PRESENTER: Benjamin Neale, PhD, from MGH, HMS & the Broad

TITLE: “Brainstorm: Integrating Genome-Wide Association Results from Neurology and Psychiatry.”

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)

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

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Brainstorm: integrating genome-wide association results from neurology and psychiatry

Benjamin Neale, Ph.D.
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BROAD INSTITUTE

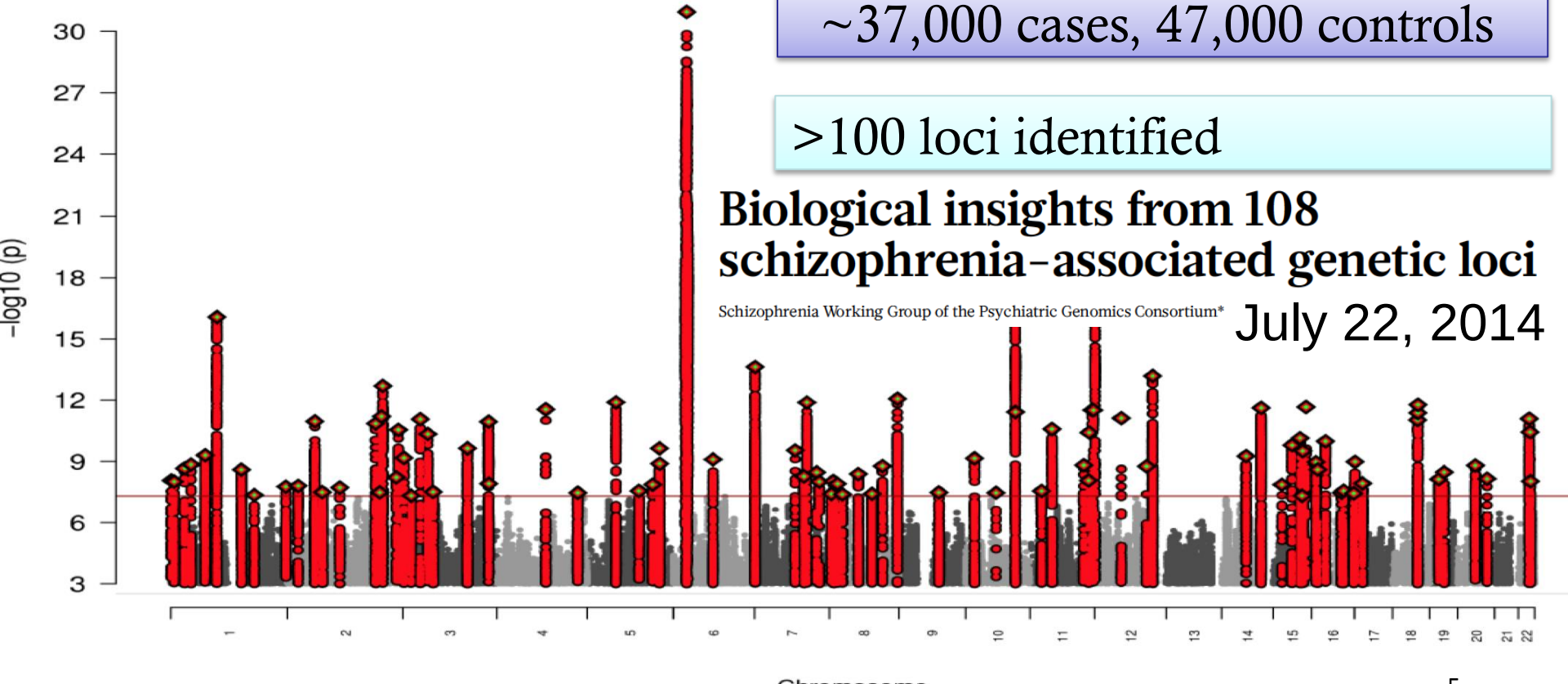
MGH 1811

CHGR

STANLEY CENTER FOR PSYCHIATRIC RESEARCH

VE RI TAS

PGC SCZ, June 2013



~37,000 cases, 47,000 controls

>100 loci identified

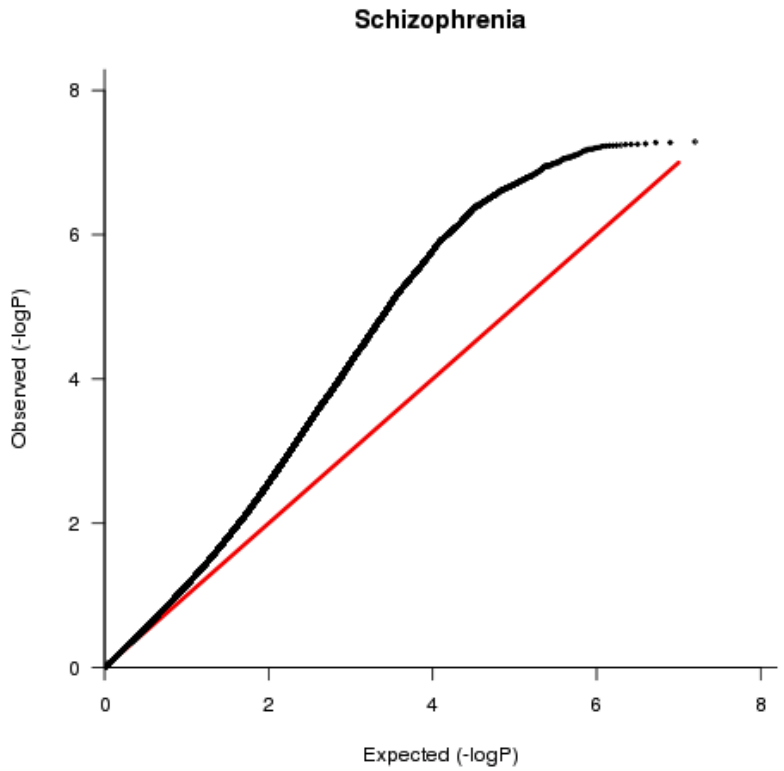
Biological insights from 108 schizophrenia-associated genetic loci

Schizophrenia Working Group of the Psychiatric Genomics Consortium*

July 22, 2014

Inflated test statistic distribution

- Strong deviation from the null
- Is this population stratification?
- Are these real effects?



LD Score regression

With thanks

Brendan Bulik-Sullivan

Hilary Finucane

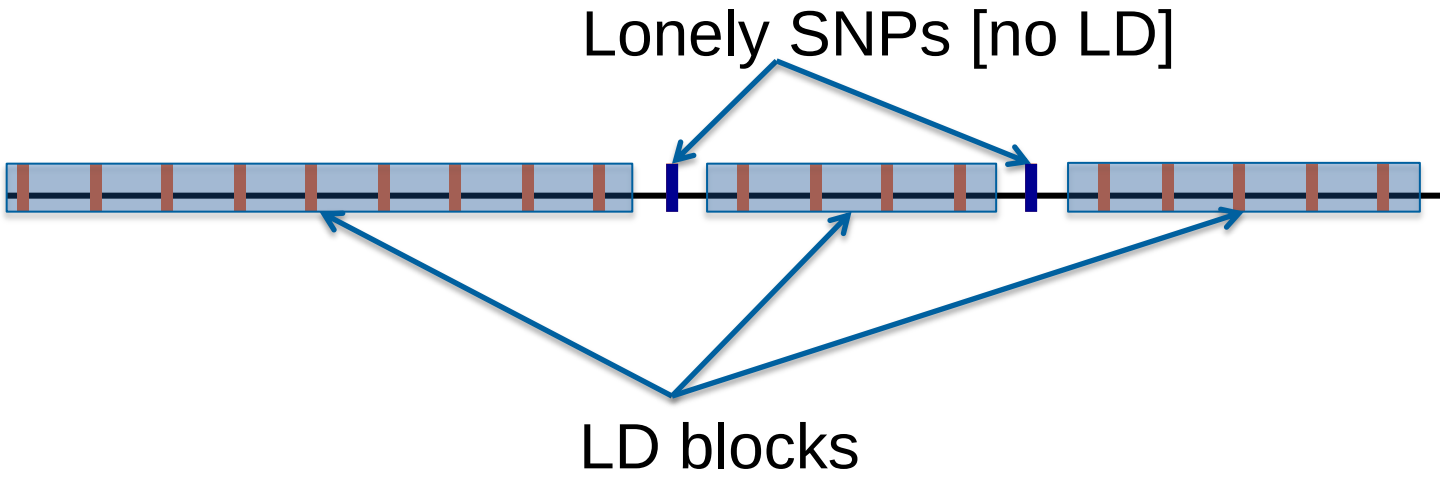
Po-Ru Loh

Mark Daly

Alkes Price

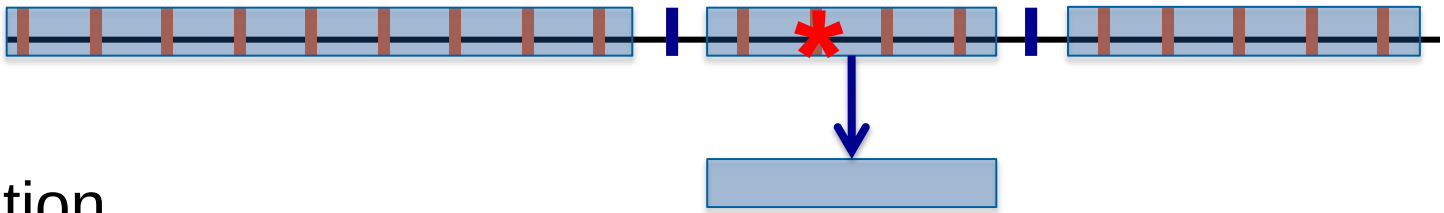
How does LD shape association?

How does LD shape association?



How does LD shape association?

- Lonely SNPs [no LD]
- LD blocks
- * Causal variants

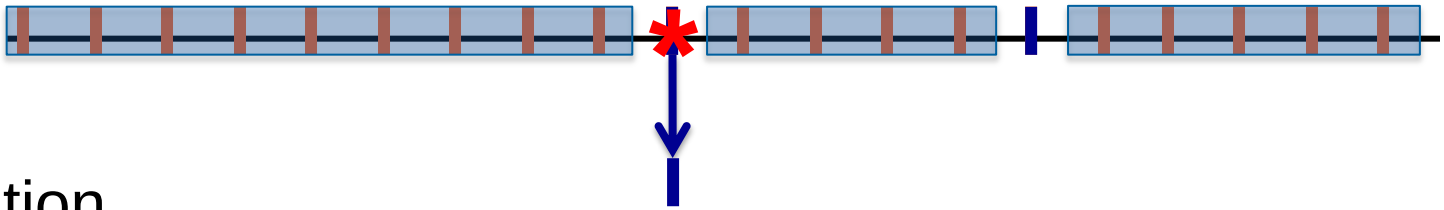


Association

All markers correlated with a causal variant show association

How does LD shape association?

- Lonely SNPs [no LD]
- LD blocks
- * Causal variants



Association

Lonely SNPs only show association if they are causal

What happens under polygenicity?

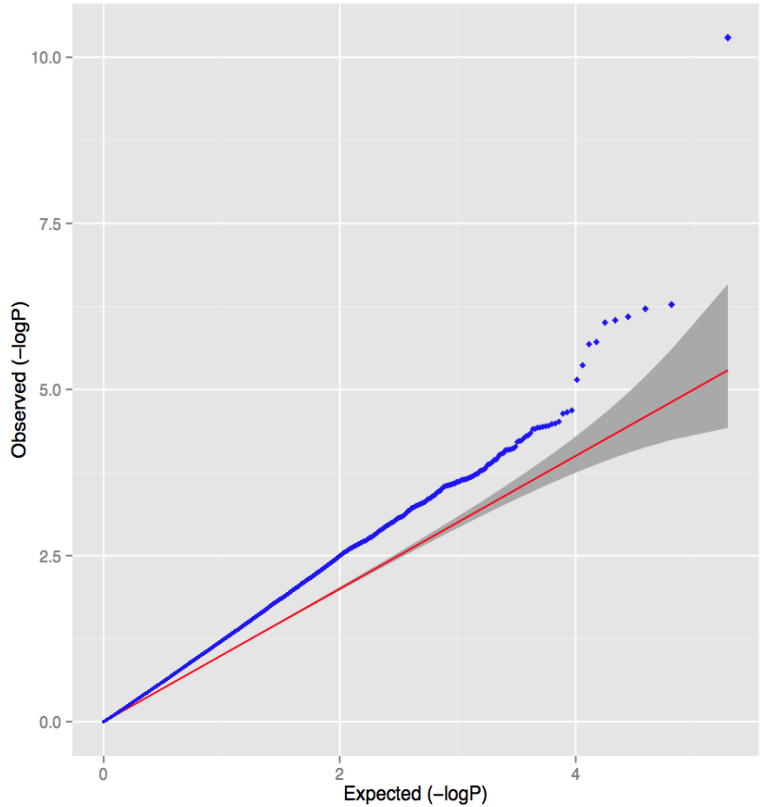
- Lonely SNPs [no LD]
- LD blocks
- * Causal variants

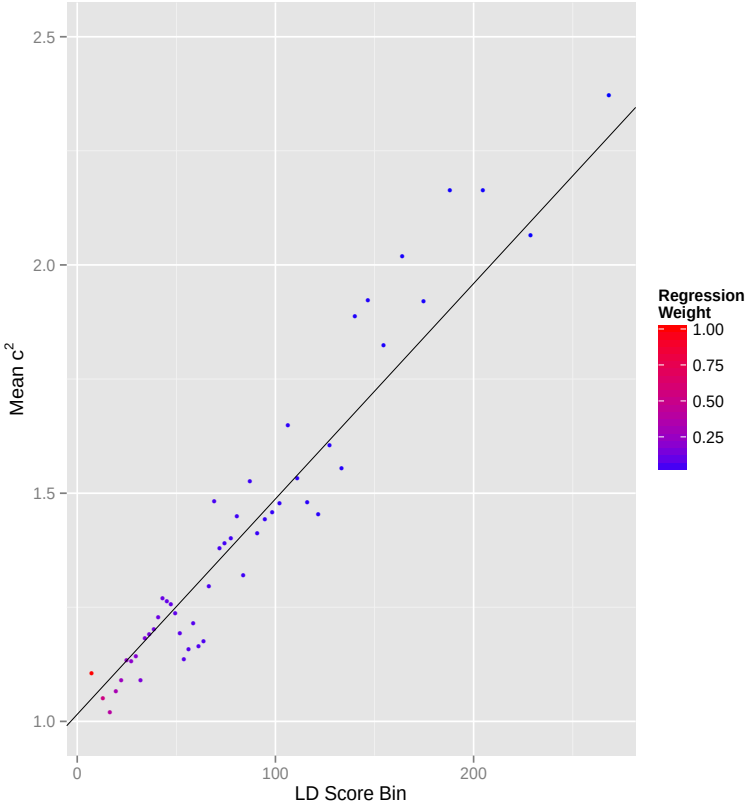
Assuming a uniform prior, we see SNPs with more LD friends showing more association

The more you tag, the more likely you are to tag a causal variant

Simulated polygenic architecture

Lambda = 1.30 LD score intercept = 1.02





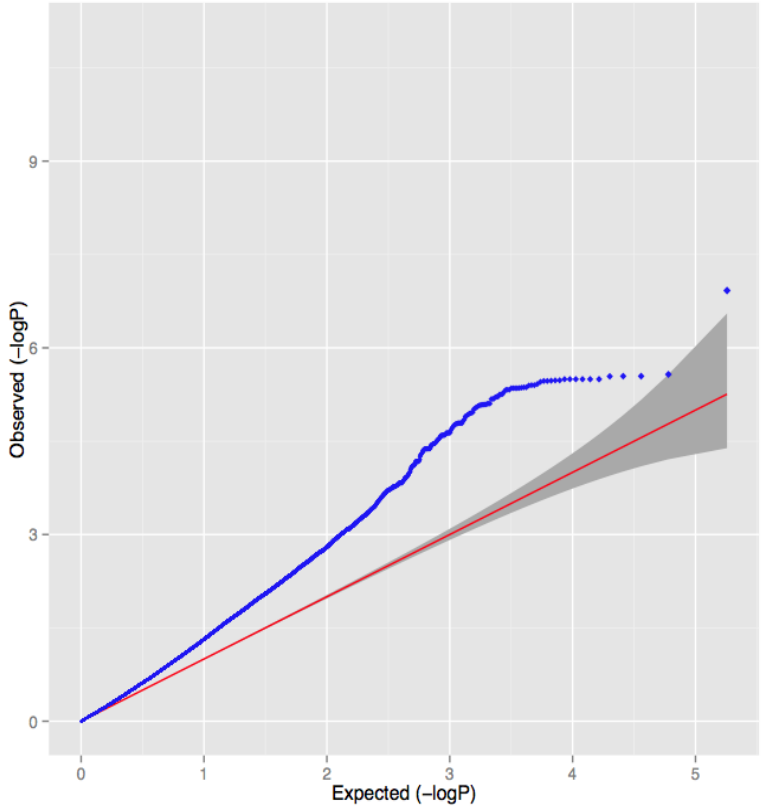
What happens under stratification?

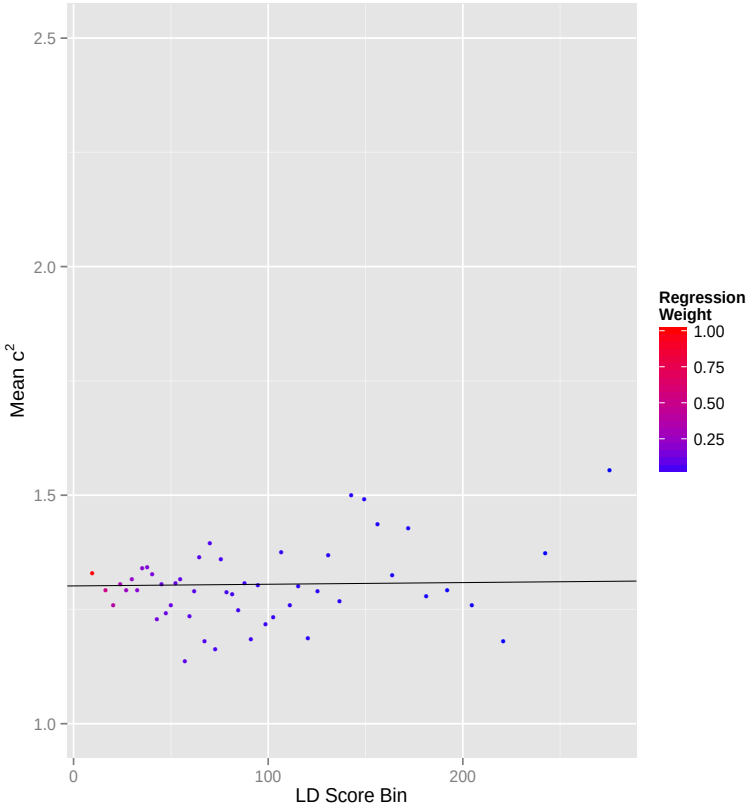
- Lonely SNPs [no LD]
- LD blocks
- * Causal variants

Under pure drift we expect LD to have no relationship to differences in allele frequencies between populations

UK controls versus Sweden controls

Lambda = 1.30 LD score intercept = 1.32





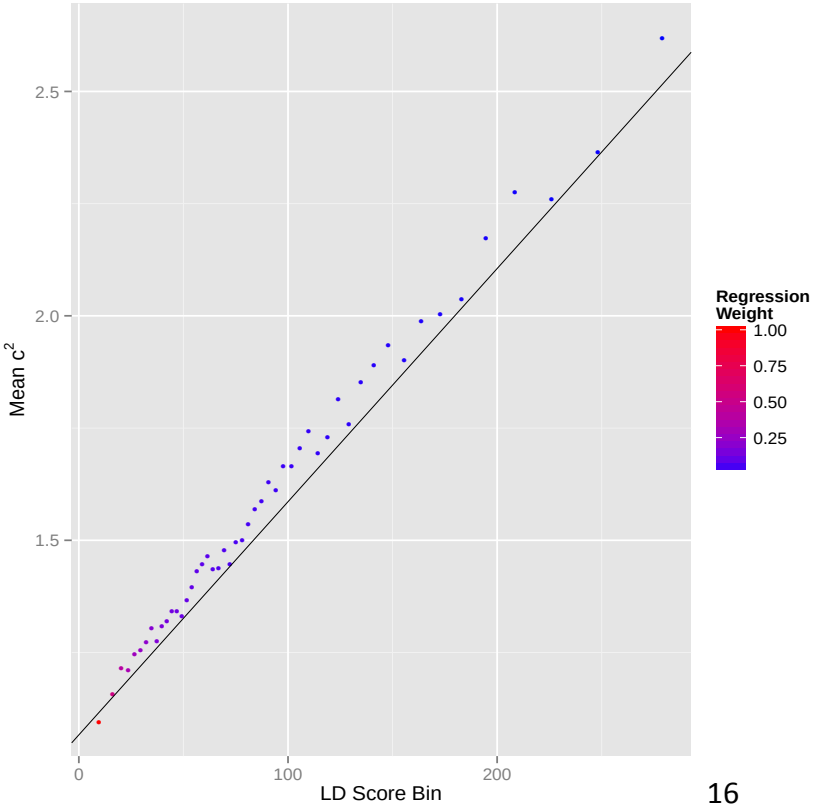
PGC Schizophrenia

Lambda = 1.48

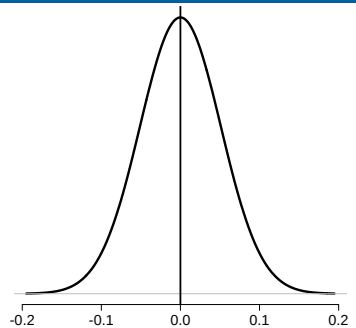
Intercept = 1.06

Slope *p*-value < 10^{-300}

Overwhelming majority of inflation is consistent with polygenic architecture



LD Score regression



Draw polygenic effects from N (0, n/m^2), var =

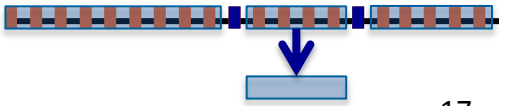
What is the E[χ^2] for variant *j*?

$$E[\chi_j^2] = 1 + Na + \frac{h_g^2 N}{M} l_j$$

New estimator of heritability

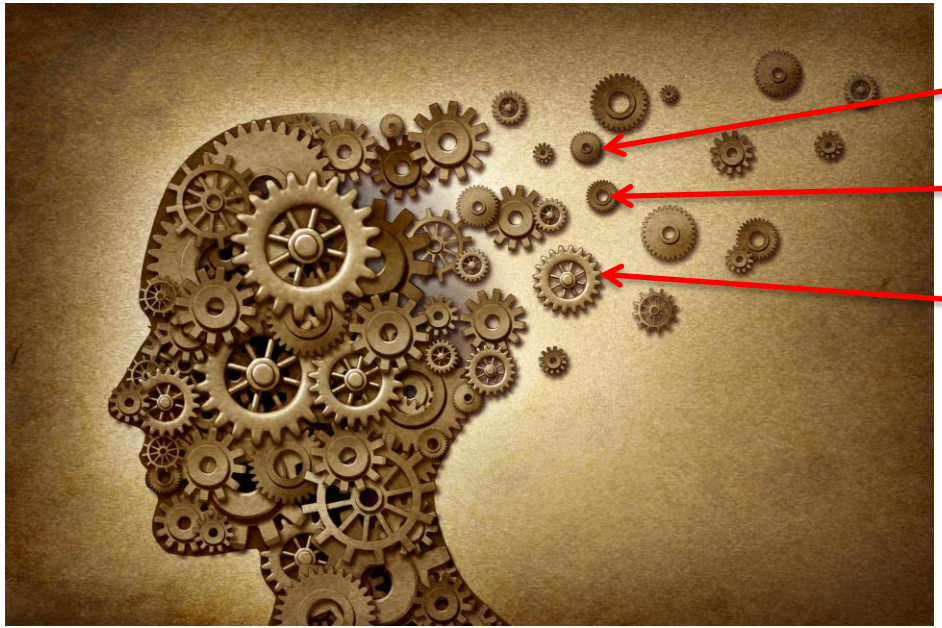
where N=sample size, M=# of SNPs, a=inflation due to confounding, h^2g is heritability (total obs.) and l_j is the *LD Score*

$$l_j = \sum_{k \neq j} r_{jk}^2$$



Bulik-Sullivan et al. Nature Genetics 2015

What about other neuropsychiatric illnesses?



Genetics?

Environment?

Social factors?

http://www.oneillinstituteblog.org/persistent-stigma-mental-illness/

Brainstorm Project






Brendan Bulik-Sullivan
Hilary Finucane
Patrick Sullivan
Bobby Koeleman
Nick Wood
Julie Williams
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Kenneth Kendler
Stephan Ripke
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Padhraig Gormley
Zhi Wei
Rainer Malik
Hailiang Huang

Andrea Byrnes
Dongmei Yu
Laramie Duncan
Kai-How Farh
Namrata Gupta
Miriam Raffeld
…and many, many others
in their respective study groups

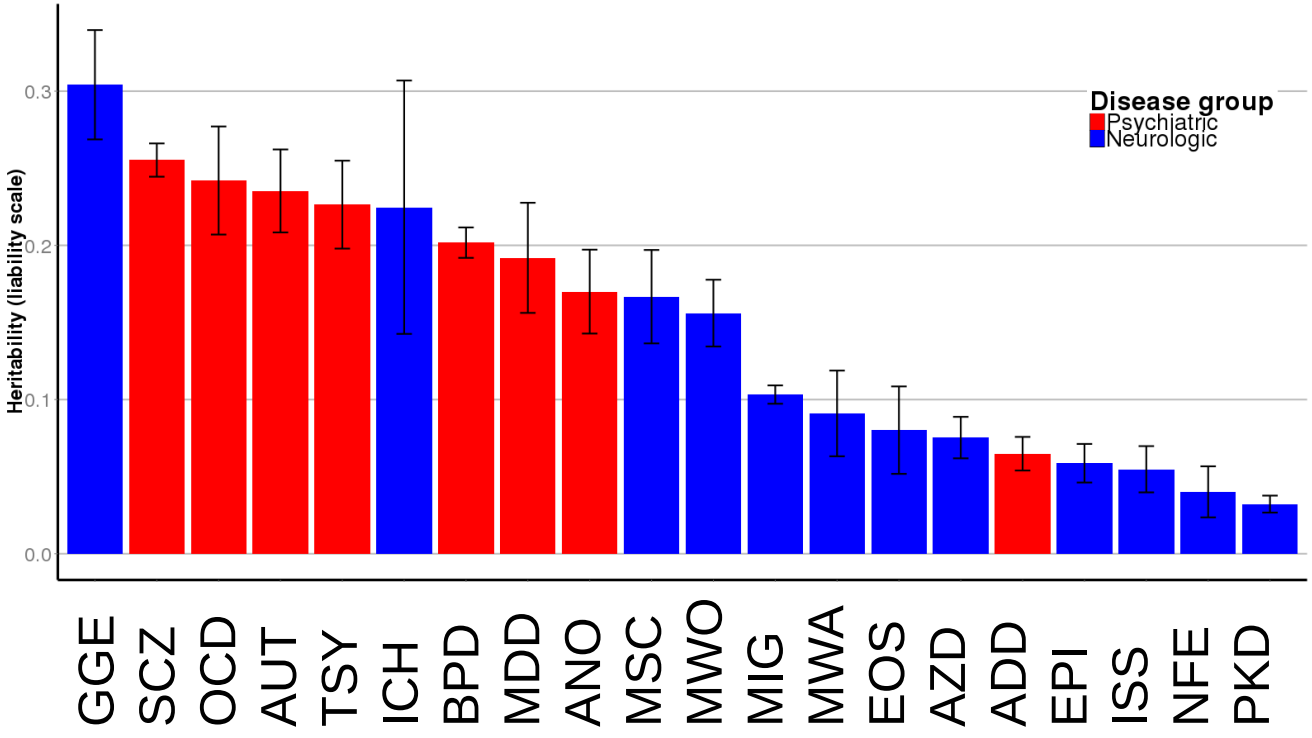
Brainstorm Project

Psychiatric Disease	Cases	Controls
ADHD	10,714	83,261
Anorexia Nervosa	3,495	11,105
Autism	5,305	5,305
Bipolar	20,352	31,358
Major depression	9,240	9,519
OCD	2,936	7,279
Schizophrenia	33,640	43,456
Tourette	4,220	8,994

Over 200,000 cases

Neurological Disease	Cases	Controls
Alzheimer	17,008	37,154
Early-onset stroke	3,274	11,012
Epilepsy	7,779	20,439
Focal Epilepsy	4,601	17,985
Generalized Epilepsy	2,525	16,244
Intracerebral hemorrhage	1,545	1,481
Ischemic stroke	10,307	19,326
Migraine	59,673	316,078
Migraine with aura	6,332	142,817
Migraine without aura	8,348	136,758
Multiple sclerosis	5,545	12,153
Parkinson	13,708	95,282

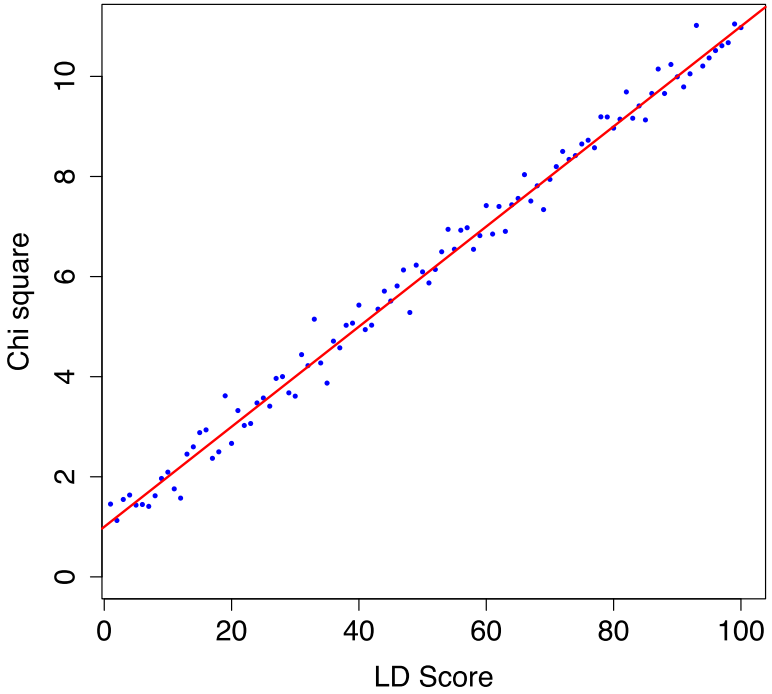
Univariate heritability from common variation



GGE = Generalized Epilepsy
SCZ = Schizophrenia
OCD = Obsessive Compulsive Disorder
AUT = Autism
TSY = Tourette's Syndrome
ICH = Intracerebral Hemorrhage
BPD = Bipolar Disorder
MDD = Major Depressive Disorder
ANO = Anorexia Nervosa
MSC = Multiple Sclerosis
MWO = Migraine without Aura
MIG = Migraine
MWA = Migraine with Aura
EOS = Early Onset Stroke
AZD = Alzheimer's Disease
ADD = Attention Deficit/Hyperactivity
EPI = Epilepsy (all)
ISS = Ischemic Stroke
NFE = Non-acquired focal epilepsy
PKD = Parkinson's Disease

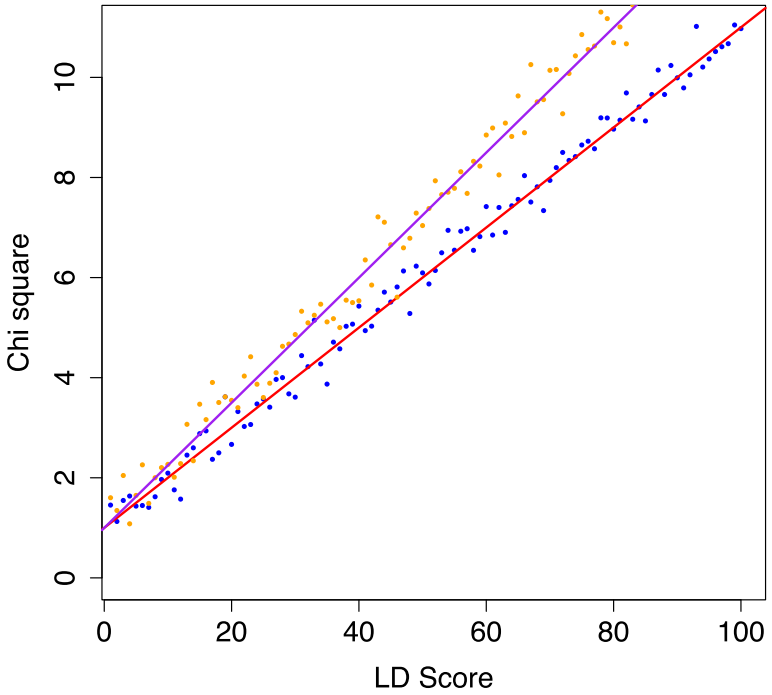
LD Score regression
Genetic correlation

Trait 1



Slope estimates heritability

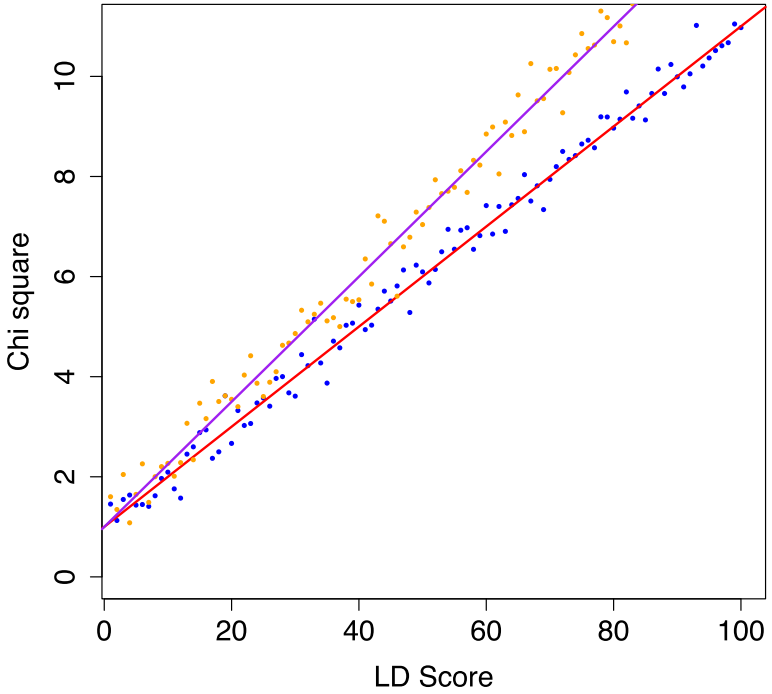
LD Score regression
Genetic correlation



Trait 1
Trait 2

We can a second trait and obtain two heritability estimates

LD Score regression
Genetic correlation

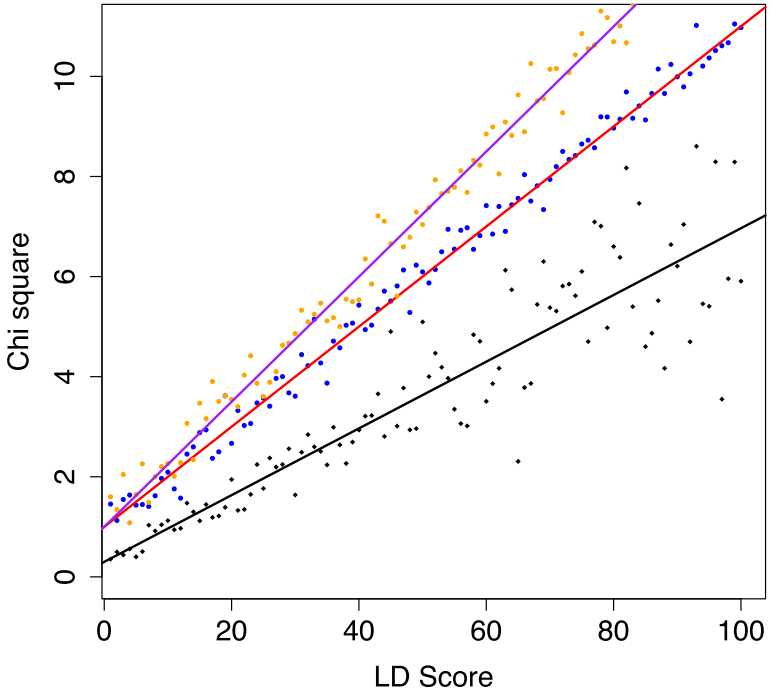


Trait 1
Trait 2

$Z^*Z = \chi^2$

So we can estimate genetic covariance from the product of the Z-scores

LD Score regression
Genetic correlation



Trait 1

Trait 2

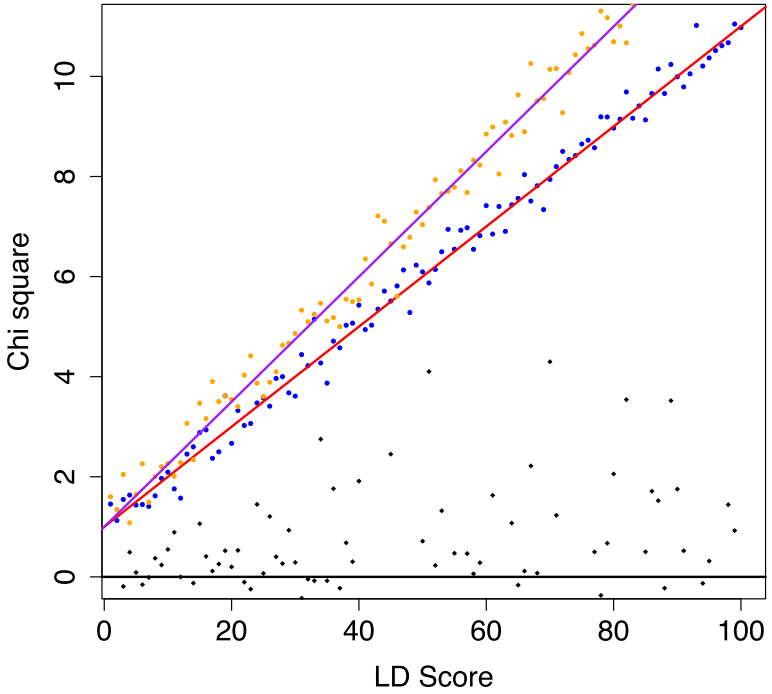
R_G

$Z^*Z = \chi^2$

So we can estimate genetic covariance from the product of the Z-scores for the two traits

$R_G = 0.5$

LD Score regression
Genetic correlation



Trait 1

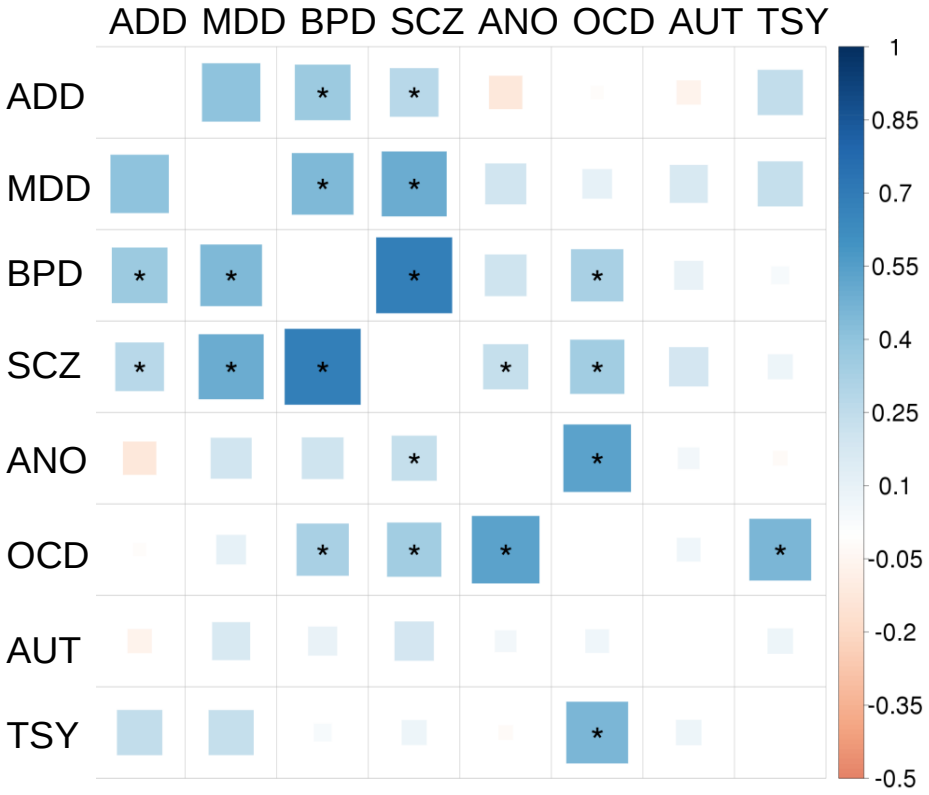
Trait 2

R_G

Here $R_G = 0$

This approach is robust to sample overlap as all variants are equally inflated

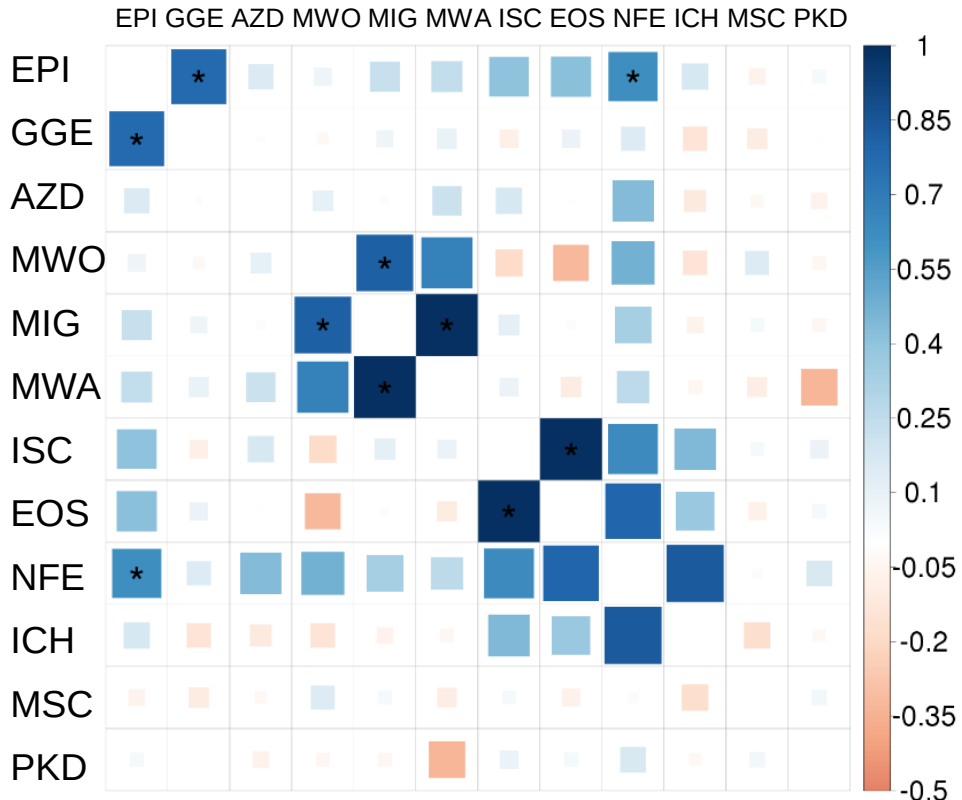
Within psychiatry



Broad sharing of common genetic risk factors across psychiatric illness

* denotes significant correlation

Within neurology

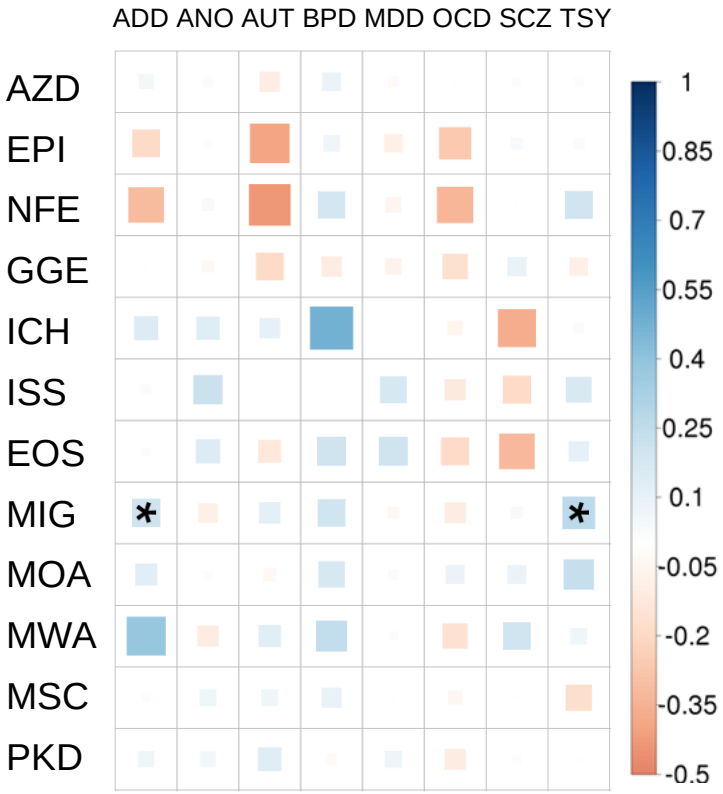


Less sharing within neurological disease than psychiatric disease

NFE genetic correlation is noisy [modest sample size]

* denotes significant correlation

Across neurology and psychiatry



Migraine shows positive genetic correlation with Tourette's Syndrome and ADHD

Limited overlap across domain

* denotes significant correlation

Conclusions

- Common variants exert influence across neurological and psychiatric disease
- Genetic risk factors in psychiatry do not respect clinical boundaries
- Limited overlap between neurology and psychiatry

Acknowledgements

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NIMH

NHGRI

All the patients, families, clinicians and study staff that make large-scale genetics studies possible