Identifying loci with different allele frequency among cases of eight psychiatric disorders with CC-GWAS

W.J. Peyrot and A.L. Price 2020 bioRxiv

World Congress of Psychiatric Genetics
October 20, 2020
Wouter Peyrot

HARVARD T.H. CHAN
SCHOOL OF PUBLIC HEALTH

PGC

Amsterdam UMC
Universitair Medische Centra

Nothing to disclose

Biological differences between psychiatric disorders are poorly understood

Relevance

- May improve distinction of clinical diagnoses
- Long-term aim: more disorder-specific treatment

Challenge

- Case-case GWAS requires individual level data
- Only Two loci associated to SCZ case vs. BIP case

SCZ = schizophrenia
BIP = bipolar disorder

No methods exist for case-case comparison based on both case-control GWAS

i.e. existing methods do not test H_0: $p_{A1} = p_{B1}$

- GWIS (Nieuwboer et al. 2015 AJHG)
  - ○ Not directly applicable to case-case comparison

- MTAG (Turley et al. 2018 Nat Genet)
  - ○ Compares case-control rather than case-case

- Disorder specific SNPs (Lee et al. 2019 Cell)
  - ○ Loci impacting both traits can have $p_{A1} \neq p_{B1}$

- mtCOJO (Zhu et al. 2018 Nat Comm; Byrne et al. 2020 Mol Psychiatry)
  - ○ Corrects for causal link of disorders on each other

See also:
Qi et al. 2018 Plos Genetics
Baselmans et al. 2019 Nat Genetics p_{A1}/ p_{B1} = allele freq. A/B cases

Outline

1. CC-GWAS method

2. Simulations

3. Application to 8 psychiatric disorders

4. Replication of empirical results

Outline

1. CC-GWAS method

2. Simulations

3. Application to 8 psychiatric disorders

4. Replication of empirical results

CC-GWAS compares cases of two disorders using case-control GWAS results
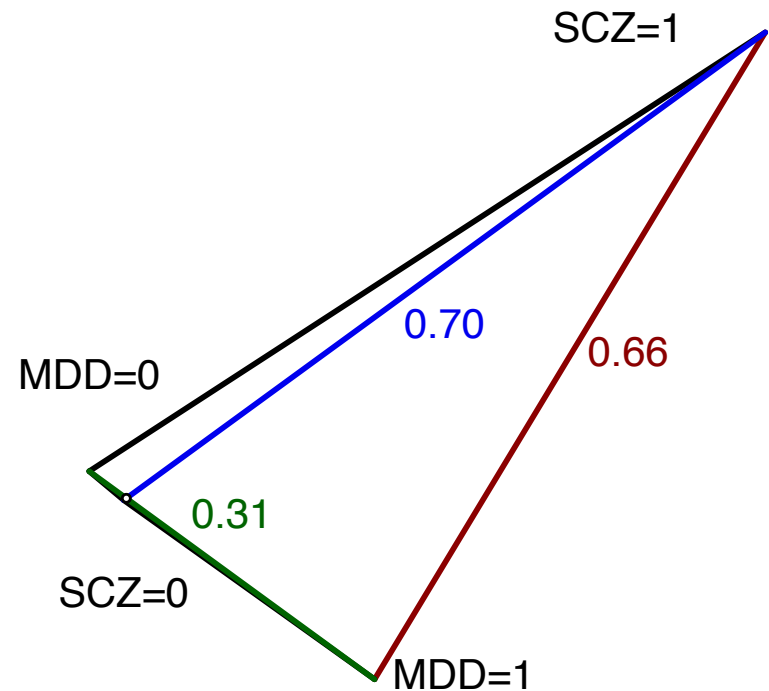
- Weighted difference between case-control GWAS results
- Combine two components

CC-GWAS compares cases of two disorders using case-control GWAS results

- Weighted difference between case-control GWAS results
- Combine two components
  1. **CC-GWAS$_{OLS}$**

     Optimizes power

CC-GWAS compares cases of two disorders using case-control GWAS results

- Weighted difference between case-control GWAS results

- Combine two components

  1. **CC-GWAS$_{OLS}$**

     Optimizes power & controls type I error at *null-null* SNPs

Null-null SNP: no impact either disorder, no case-case difference

CC-GWAS compares cases of two disorders using case-control GWAS results

- Weighted difference between case-control GWAS results

- Combine two components

    1. **CC-GWAS$_{OLS}$**

       Optimizes power & controls type I error at *null-null* SNPs

    2. **CC-GWAS$_{Exact}$**

       Controls type I error at *stress test* SNPs

Null-null SNP: no impact either disorder, no case-case difference
Stress test SNP: impacts both disorders, no case-case difference

CC-GWAS compares cases of two disorders using case-control GWAS results

- Weighted difference between case-control GWAS results

- Combine two components

  1. **CC-GWAS$_{OLS}$**

     Optimizes power & controls type I error at *null-null* SNPs

  2. **CC-GWAS$_{Exact}$**

     Controls type I error at *stress test* SNPs

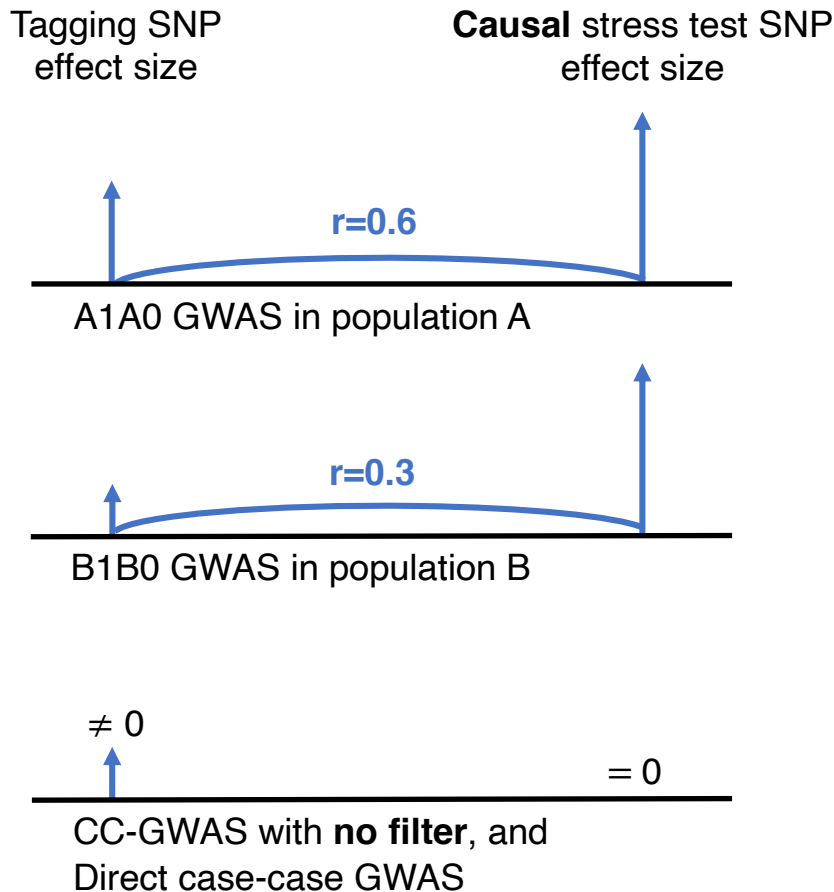→ Significant when p-OLS < 5×10^{-8} **and** p-Exact < 10^{-4}

Null-null SNP: no impact either disorder, no case-case difference
Stress test SNP: impacts both disorders, no case-case difference

CC-GWAS filters false positives due to differential tagging of a causal stress test SNP
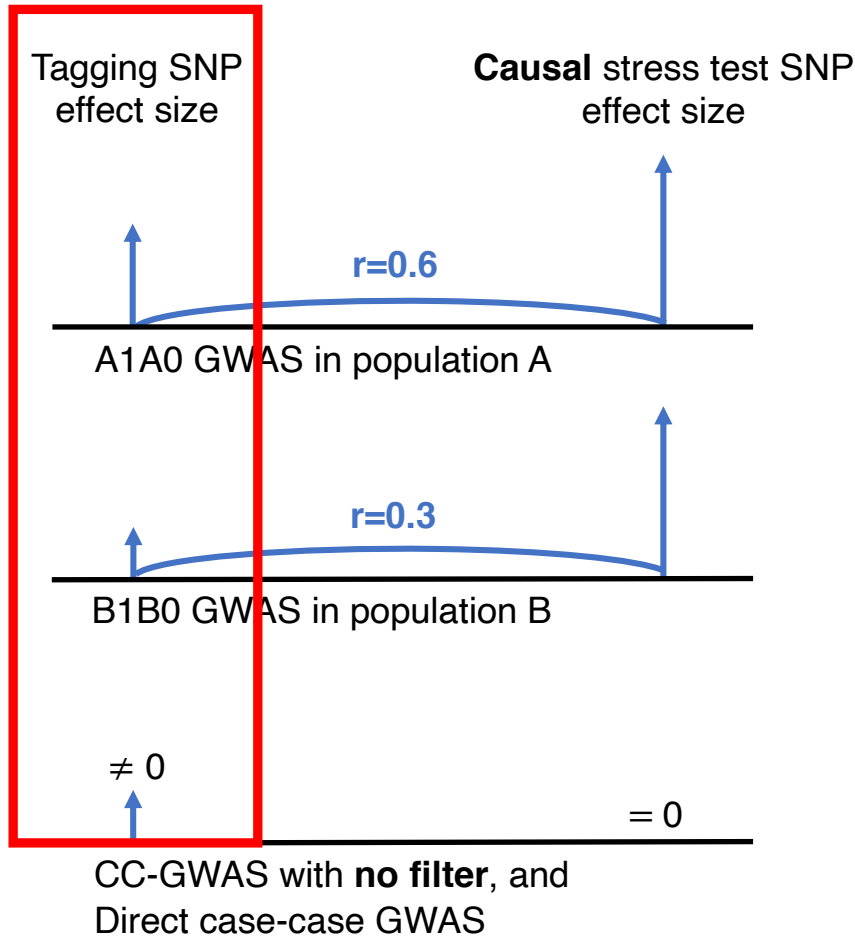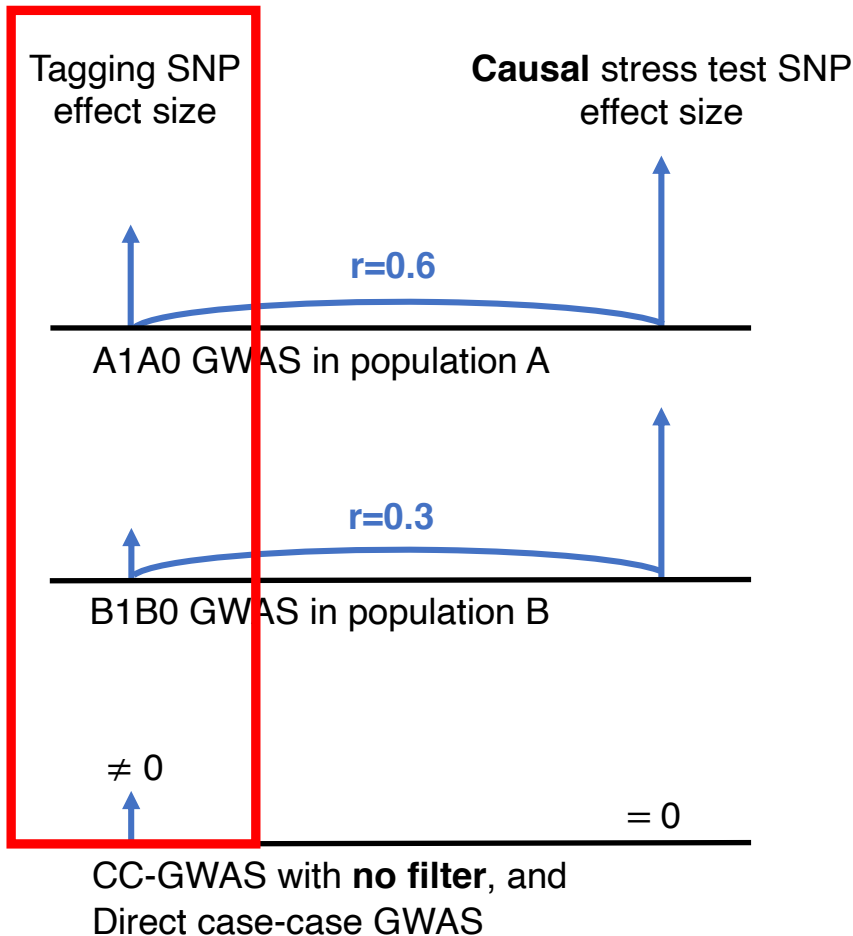
• Subtle ancestry differences may result in differential tagging of a causal stress test SNP across both case-control GWAS

CC-GWAS filters false positives due to differential tagging of a causal stress test SNP

A. Illustrative example

B. Simulation

Tagging SNP effect size

Causal stress test SNP effect size

A. Illustrative example

r=0.6

A1A0 GWAS in population A

r=0.3

B1B0 GWAS in population B

$\neq 0$

$= 0$

CC-GWAS with **no filter**, and Direct case-case GWAS

- Subtle ancestry differences may result in differential tagging of a causal stress test SNP across both case-control GWAS

B. Simulation

CC–G
Direc
CC–G
CC–G

N multiplier

N multiplier

CC-GWAS filters false positives due to differential tagging of a causal stress test SNP

A. Illustrative example

B. Simulation

Tagging SNP effect size

Causal stress test SNP effect size

A. Illustrative example

r=0.6

A1A0 GWAS in population A

r=0.3

B1B0 GWAS in population B

$\neq 0$

$= 0$

CC-GWAS with **no filter**, and Direct case-case GWAS

- Subtle ancestry differences may result in differential tagging of a causal stress test SNP across both case-control GWAS

potential false positive

CC-GWAS filters false positives due to differential tagging of a causal stress test SNP

A. Illustrative example

B. Simulation

Tagging SNP effect size

Causal stress test SNP effect size

A. Illustrative example

r=0.6

A1A0 GWAS in population A

r=0.3

B1B0 GWAS in population B

≠ 0

= 0

CC-GWAS with **no filter**, and Direct case-case GWAS

0.4

1e-4

5e-8

B. Simulation

0.5   1   2   5

N multiplier

1e-2

CC–C
Direc
CC–C
CC–C

- Subtle ancestry differences may result in differential tagging of a causal stress test SNP across both case-control GWAS

- CC-GWAS screens region around candidate CC-GWAS SNP → filters when evidence of differential tagging is found

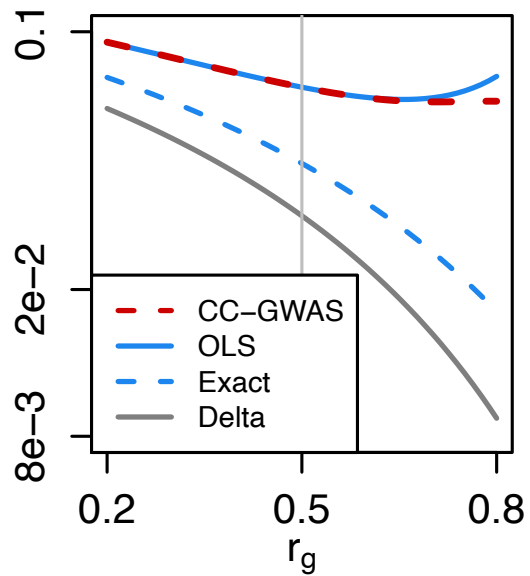= advantage of CC-GWAS over direct case-case comparison

potential false positive

Outline

1. CC-GWAS method

2. Simulations

3. Application to 8 psychiatric disorders

4. Replication of empirical results
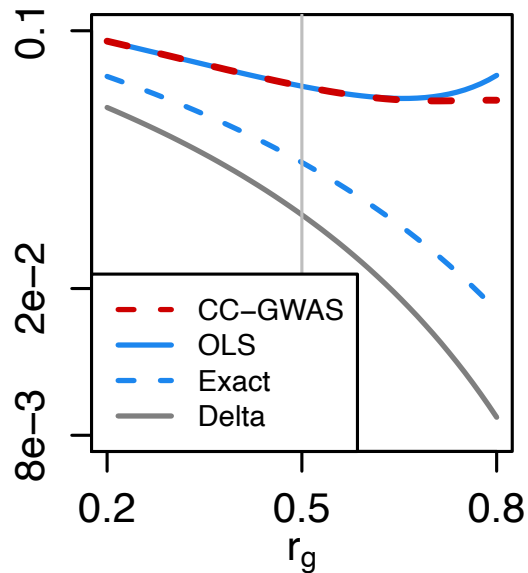
CC-GWAS:
Is well powered

A. Power

$h_{l,A}^2 = 0.2; K_A = 0.01; N_{A1} = N_{A0} = 100k$
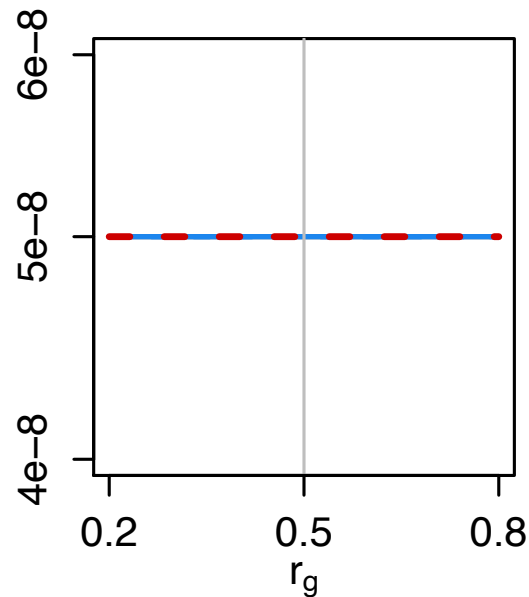$h_{l,B}^2 = 0.1; K_B = 0.15; N_{B1} = N_{B0} = 100k$
$r_g = 0.5; m = 5e3$

CC-GWAS:
Controls type I error at *null-null* SNPs

A. Power

B. Type I error
(null–null SNPs)

Legend:
- CC–GWAS (red dashed)
- OLS (blue solid)
- Exact (blue dashed)
- Delta (gray solid)
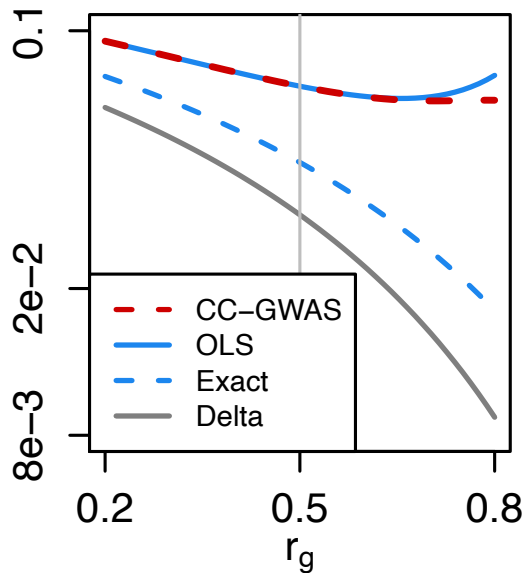
Null-null SNP: no impact either disorder, no case-case difference

$h_{l,A}^2 = 0.2; K_A = 0.01; N_{A1} = N_{A0} = 100k$

$h_{l,B}^2 = 0.1; K_B = 0.15; N_{B1} = N_{B0} = 100k$
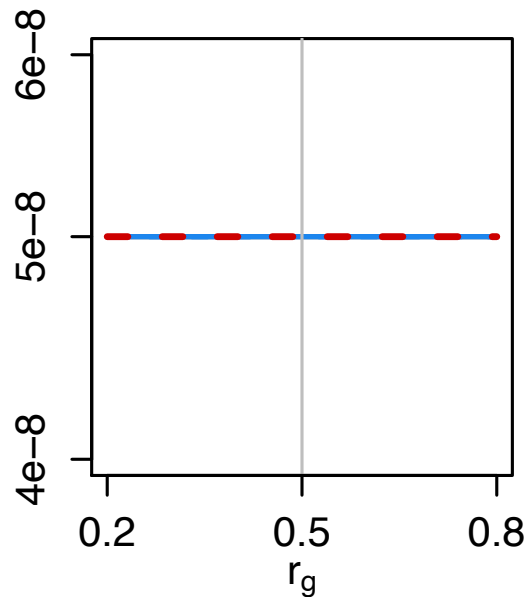
$r_g = 0.5; m = 5e3$

CC-GWAS:
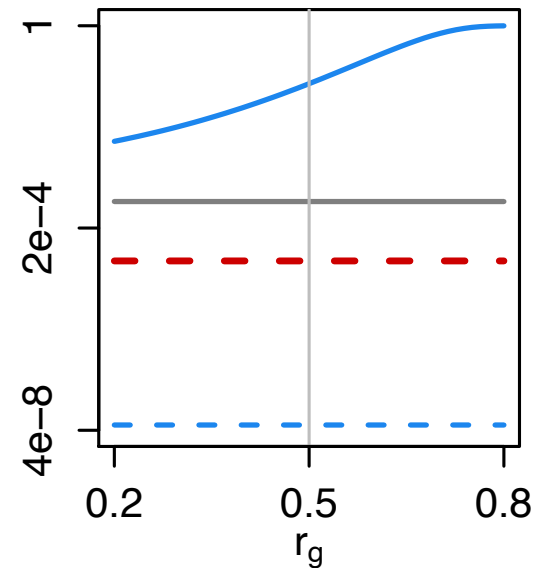## Controls type I error at *stress test* SNPs

A. Power

B. Type I error
(null–null SNPs)

C. Type I error
(stress test SNPs)

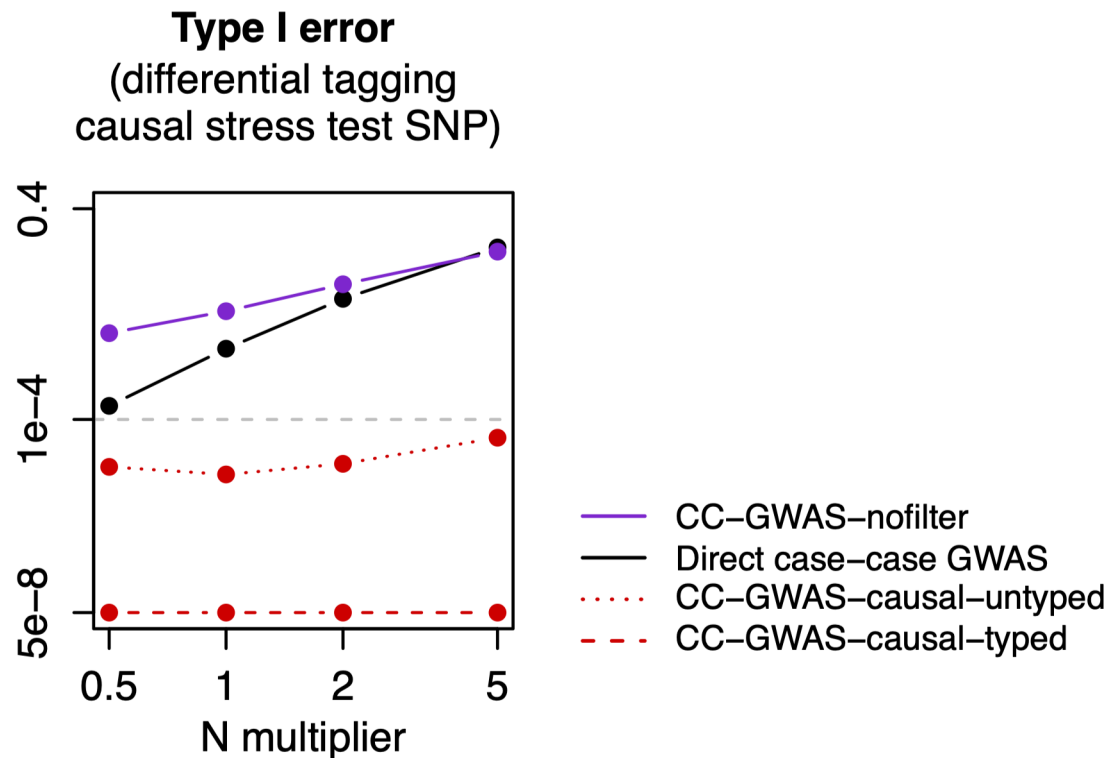*Stress test* SNP: impacts both disorders, no case-case difference

Stress test SNPs explain 0.1% variance in A
$h_{l,A}^2 = 0.2; K_A = 0.01; N_{A1} = N_{A0} = 100k$
$h_{l,B}^2 = 0.1; K_B = 0.15; N_{B1} = N_{B0} = 100k$
$r_g = 0.5; m = 5e3$

CC-GWAS: controls type I error due to *differential tagging of a causal stress test SNP*

Type I error
(differential tagging causal stress test SNP)

Legend:
- CC–GWAS–nofilter
- Direct case–case GWAS
- CC–GWAS–causal–untyped
- CC–GWAS–causal–typed

X-axis: N multiplier

Stress test SNPs explain 0.1% variance in A
$h_{l,A}^2 = 0.2; K_A = 0.01; N_{A1} = N_{A0} = 100k$
$h_{l,B}^2 = 0.1; K_B = 0.15; N_{B1} = N_{B0} = 100k$
$r_g = 0.5; m = 5e3$

Stress test SNP: impacts both disorders, no case-case difference

Simulations based on real-life LD patters in 25k UKB British vs. 25k UKB non-British

Outline

CC-GWAS identifies 196 loci distinguishing cases of 8 psychiatric disorders

SCZ, BIP and MDD

- 121 loci summed across 3 pairs → 116 independent loci
- 21 CC-GWAS-specific loci (=not significant in case-control GWAS)

SCZ, schizophrenia; BIP, bipolar disorder; MDD, major depressive disorder; ADHD, attention deficit/hyperactivity disorder; AN, anorexia nervosa; ASD, autism spectrum disorder; OCD, obsessive–compulsive disorder; TS, Tourette's Syndrome

CC-GWAS identifies 196 loci distinguishing cases of 8 psychiatric disorders

SCZ, BIP and MDD

- 121 loci summed across 3 pairs → 116 independent loci
- 21 CC-GWAS-specific loci (=not significant in case-control GWAS)

SCZ, BIP, MDD, ADHD, AN, ASD, OCD and TS

- 313 loci summed across 28 pairs → 196 independent loci
- 72 CC-GWAS-specific loci (=not significant in case-control GWAS)

SCZ, schizophrenia; BIP, bipolar disorder; MDD, major depressive disorder; ADHD, attention deficit/hyperactivity disorder; AN, anorexia nervosa; ASD, autism spectrum disorder; OCD, obsessive–compulsive disorder; TS, Tourette's Syndrome

Most CC-GWAS loci in comparisons with SCZ cases (most powerful case-control GWAS)

# loci	SCZ	BIP	MDD	ADHD	ANO	ASD	OCD	TS
SCZ	-	12 (7)	99 (10)	43 (14)	41 (5)	40 (10)	0 (0)	13 (4)
BIP		-	10 (4)	8 (6)	5 (2)	3 (0)	1 (1)	5 (3)
MDD			-	9 (2)	6 (1)	3 (2)	0 (0)	0 (0)
ADHD				-	4 (3)	1 (0)	2 (2)	2 (2)
AN					-	1 (1)	0 (0)	2 (1)
ASD						-	1 (1)	1 (1)
OCD							-	1 (1)
TS								-

() = CC-GWAS-specific, i.e. not significant in input case-control GWAS results

SCZ, schizophrenia; BIP, bipolar disorder; MDD, major depressive disorder; ADHD, attention deficit/hyperactivity disorder; AN, anorexia nervosa; ASD, autism spectrum disorder; OCD, obsessive–compulsive disorder; TS, Tourette's Syndrome

Most CC-GWAS loci in comparisons with SCZ cases (most powerful case-control GWAS)

| # loci	SCZ	BIP	MDD	ADHD	ANO	ASD	OCD	TS
SCZ	-	12 (7)	99 (10)	43 (14)	41 (5)	40 (10)	0 (0)	13 (4)
BIP		-	10 (4)	8 (6)	5 (2)	3 (0)	1 (1)	5 (3)
MDD			-	9 (2)	6 (1)	3 (2)	0 (0)	0 (0)
ADHD				-	4 (3)	1 (0)	2 (2)	2 (2)
AN					-	1 (1)	0 (0)	2 (1)
ASD						-	1 (1)	1 (1)
OCD							-	1 (1)
TS								-

() = CC-GWAS-specific, i.e. not significant in input case-control GWAS results

SCZ, schizophrenia; BIP, bipolar disorder; MDD, major depressive disorder; ADHD, attention deficit/hyperactivity disorder; AN, anorexia nervosa; ASD, autism spectrum disorder; OCD, obsessive–compulsive disorder; TS, Tourette's Syndrome

CC-GWAS identifies 12 SCZ vs. BIP loci

			Number of significant loci			
					CC-GWAS	
A1A0	B1B0	OLS weights	A1A0	B1B0	**all**	**specific**
SCZ (41k/65k)	BIP (20k/31k)	0.55/-0.43	139	15	**12**	7

specific = not significant in A1A0/B1B0
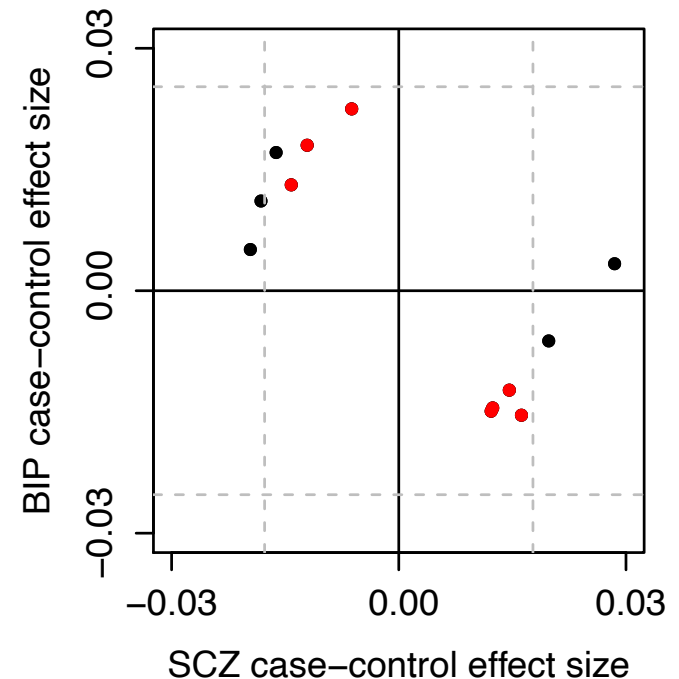
Using case-control summary statistics from:
Pardinas et al. 2018 Nat Genetics for SCZ
Stahl et al. 2019 Nat Genetics for BIP
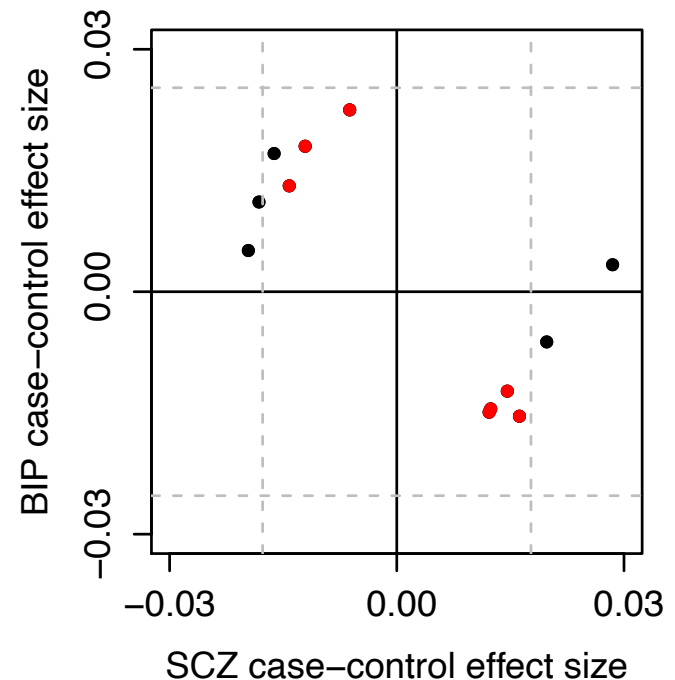
CC-GWAS identifies 12 SCZ vs. BIP loci

			Number of significant loci		CC-GWAS	
					CC-GWAS	
A1A0	B1B0	OLS weights	A1A0	B1B0	**all**	**specific**
SCZ (41k/65k)	BIP (20k/31k)	0.55/-0.43	139	15	**12**	**7**

specific = not significant in A1A0/B1B0

Ruderfer et al. 2018 Cell
- 24k SCZ cases vs. 15k BIP cases
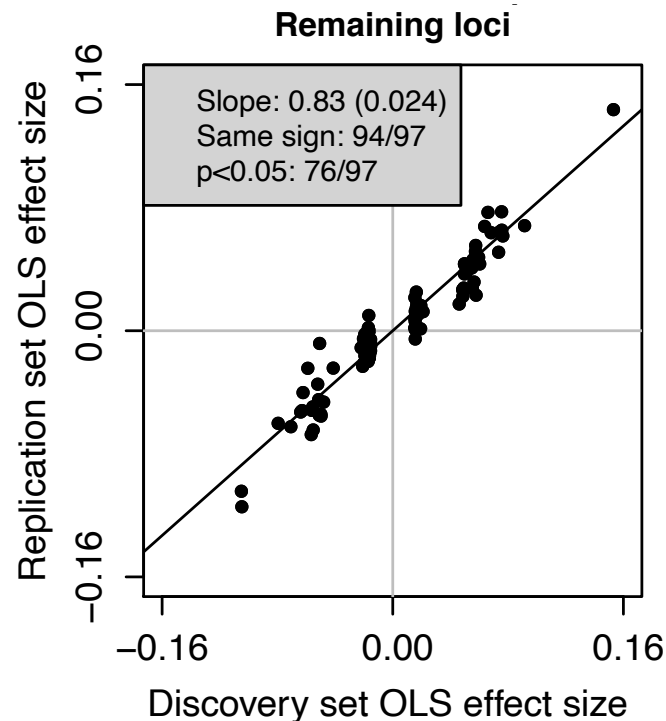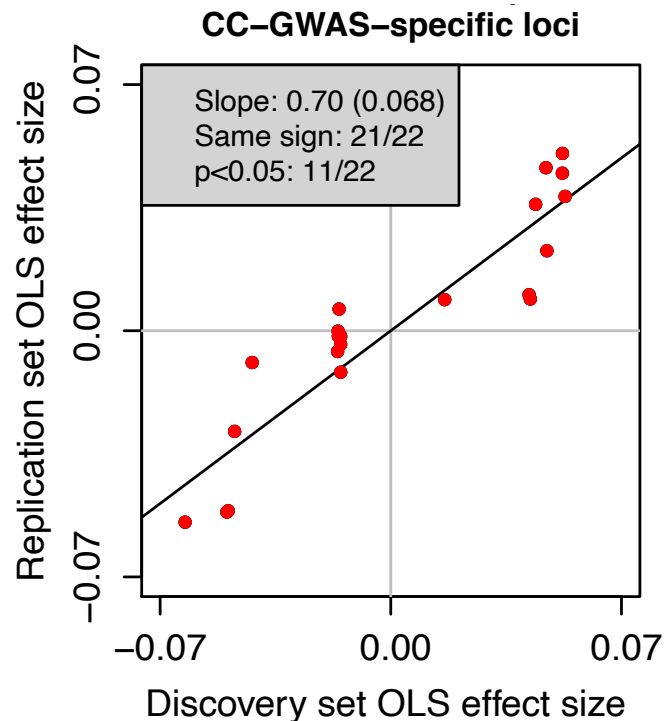- 2 loci
- rg = 1.02 (0.02)

CC-GWAS-specific loci implicate role of Kruppel Like Factors in Schizophrenia

- SCZ vs. BIP lead SNP in exon *KLF16* (chr 19)

- SCZ vs. MDD lead SNP in exon *KLF6* (chr 10)

- *KLF* play role in DNA-binding transcription factor activity

- May play role in neurite outgrowth & axon regeneration

Moore DL et al. 2011 Mol. Cell. Neurosci

Outline

1. CC-GWAS method

2. Simulations

3. Application to 8 psychiatric disorders

4. Replication of empirical results

CC-GWAS results replicate well in independent data

CC–GWAS–specific loci

Slope: 0.70 (0.068)
Same sign: 21/22
p<0.05: 11/22

Remaining loci

Slope: 0.83 (0.024)
Same sign: 94/97
p<0.05: 76/97

SCZ vs. MDD and 3 comparisons of 3 autoimmune diseases (Crohn's disease, Ulcerative colitis, Rheumatoid arthritis)

Conclusion

1. CC-GWAS compares cases of two disorders based on the respective case-control GWAS results

2. CC-GWAS attains good power and accurate type I error control

3. CC-GWAS identifies 196 loci distinguishing cases of eight psychiatric disorders, including 72 CC-GWAS-specific loci

4. CC-GWAS results replicate well in independent data

10.1101/2020.03.04.9

bioRxiv

Thank you

Alkes Price

PGC working groups of SCZ, BIP,
MDD, ADHD, AN, ASD, and OCD&TS

Douglas Ruderfer
Armin Schoech
Omer Weissbrod
Luke 'O Connor
Steven Gazal
Jordan Smoller
Eli Stahl
Naomi Wray
Kenneth Kendler
James Walters
Enda Byrne
Andrew McQuillin
Arianna Di Florio

Contact:
wpeyrot@hsph.harvard.edu

HARVARD T.H. CHAN
SCHOOL OF PUBLIC HEALTH

PGC

Amsterdam UMC
Universitair Medische Centra