PGC Worldwide Lab Call Details

DATE: Friday, April 11th, 2014
PRESENTER: Ole A. Andreassen, University of Oslo
TITLE: "Boosting the Power of Psychiatric GWAS with New Statistical Tools"
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
0000 AEST – Australia (Friday, March 14th into Saturday, March 15th, 2014)
DURATION: 1 hour

TELEPHONE:
- US Toll free: 1 866 515.2912
- International direct: +1 617 399.5126
- Toll-free number? See http://www.btconferencing.com/globalaccess/?bid=75_public
- 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: 275 694 38 then #

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, May 9th, 2014
PRESENTER: TBD
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
0000 AEST – Australia (Saturday, May 10th, 2014)
DURATION: 1 hour

TELEPHONE:
- US Toll free: 1 866 515.2912
- International direct: +1 617 399.5126
- Toll-free number? See http://www.btconferencing.com/globalaccess/?bid=75_public
- 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: 275 694 38 then #

Boosting the power of psychiatric GWAS with new statistical tools

PGC World Wide Lab Meeting April 11, 2014

Ole A. Andreassen, Yunpeng Wang, Andrew Schork, Wes Thompson, Anders M. Dale, PGC Groups.

Univ of Oslo and UCSD

Outline

I. Genomic annotation enrichment
II. Pleiotropy enrichment
III. Increased discovery & replication
IV. Improved prediction

The case of the missing heritability

When scientists opened up the human genome, they expected to find the genetic components of common traits and diseases. But they were nowhere to be seen.

nature genetics

Common SNPs explain a large proportion of the heritability for human height

Jian Yang[1], Beben Benyamin[1], Brian P McEvoy[1], Scott Gordon[1], Anjali K Henders[1], Dale R Nyholt[1], Pamela A Madden[2], Andrew C Heath[2], Nicholas G Martin[1], Grant W Montgomery[1], Michael E Goddard[3] & Peter M Visscher[1]

LETTERS

Common polygenic variation contributes to risk of schizophrenia and bipolar disorder

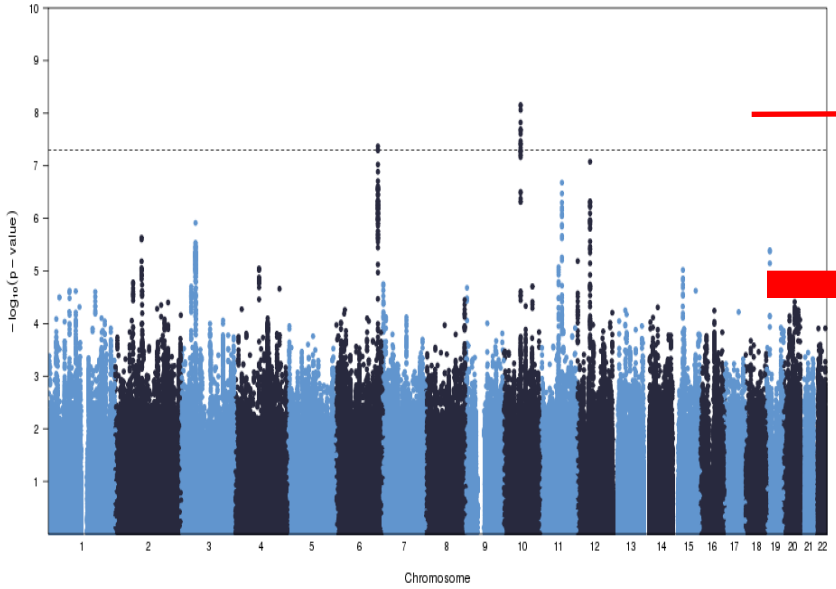
The International Schizophrenia Consortium*

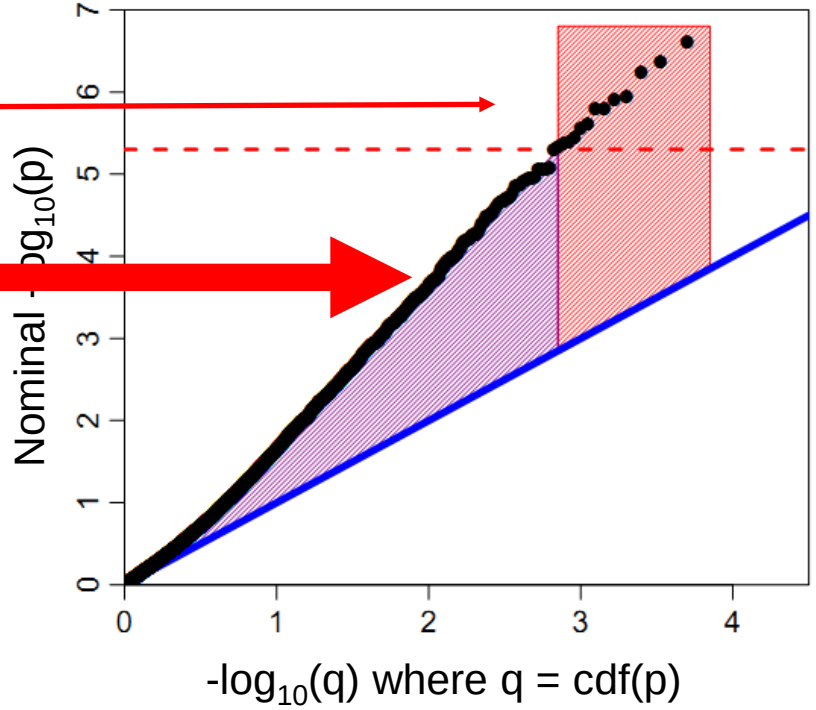
Complex disorders – polygenic architecture

- High number of SNPs each with a small effect
  - 2000 SNPs in Schizophernia? (Ripke et al 2013)
- Difficult to detect, need extremely large GWAS
  - 2-3 millions?

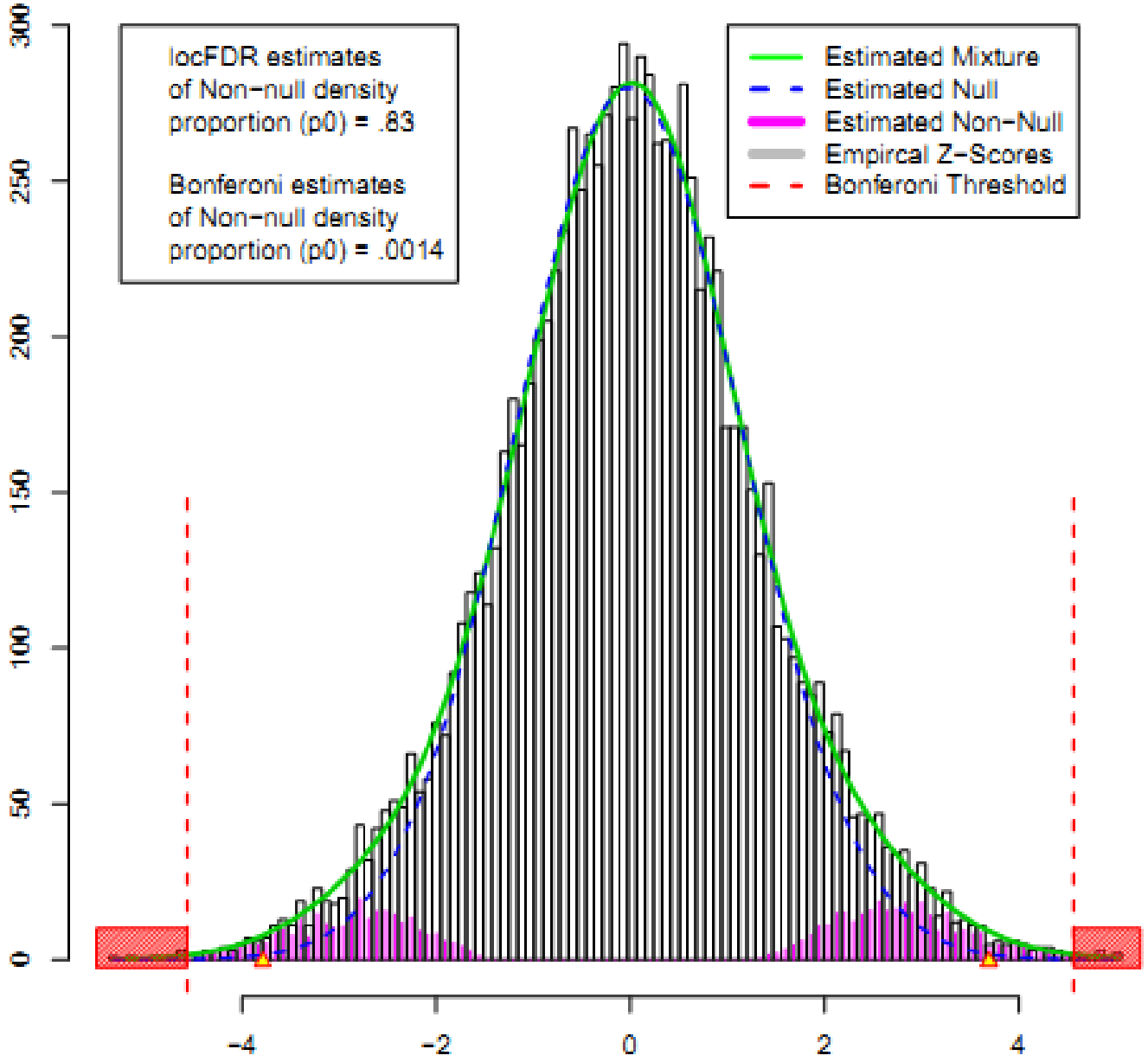
Can be detected with improved statistical approaches?

Manhattan - Q-Q Plots



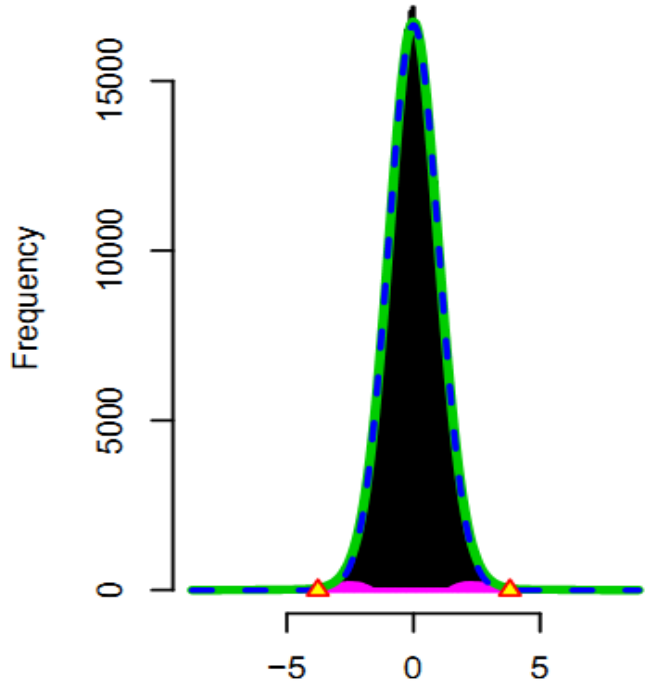


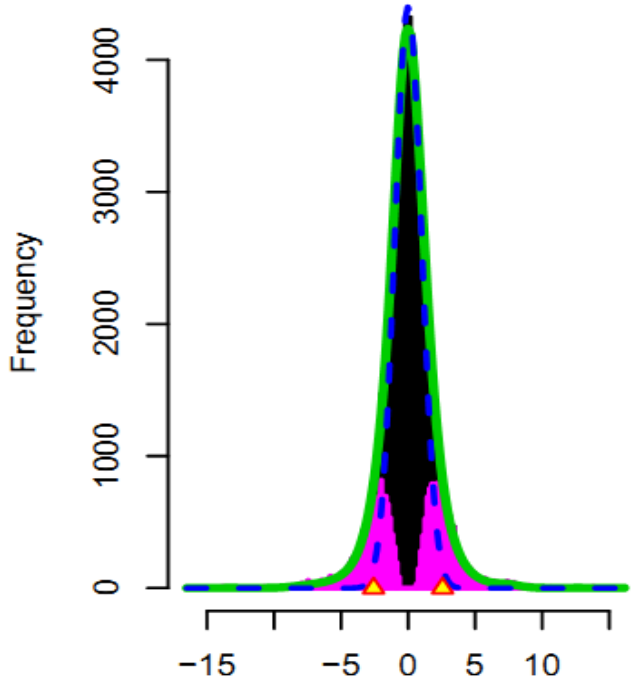
Mixture distribution



Are all SNPs created equal?

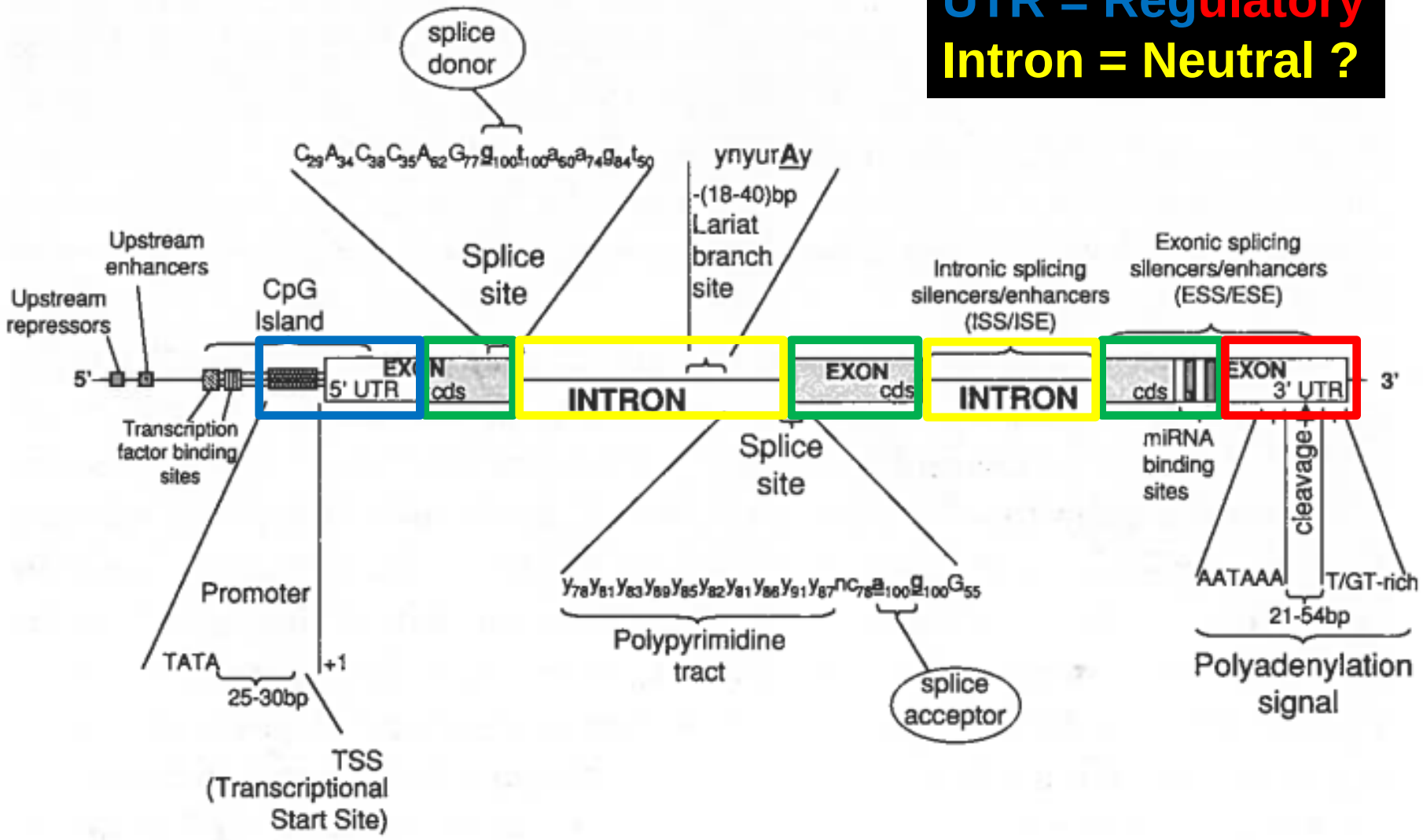
- Estimate priors: enrich the non-null SNPs





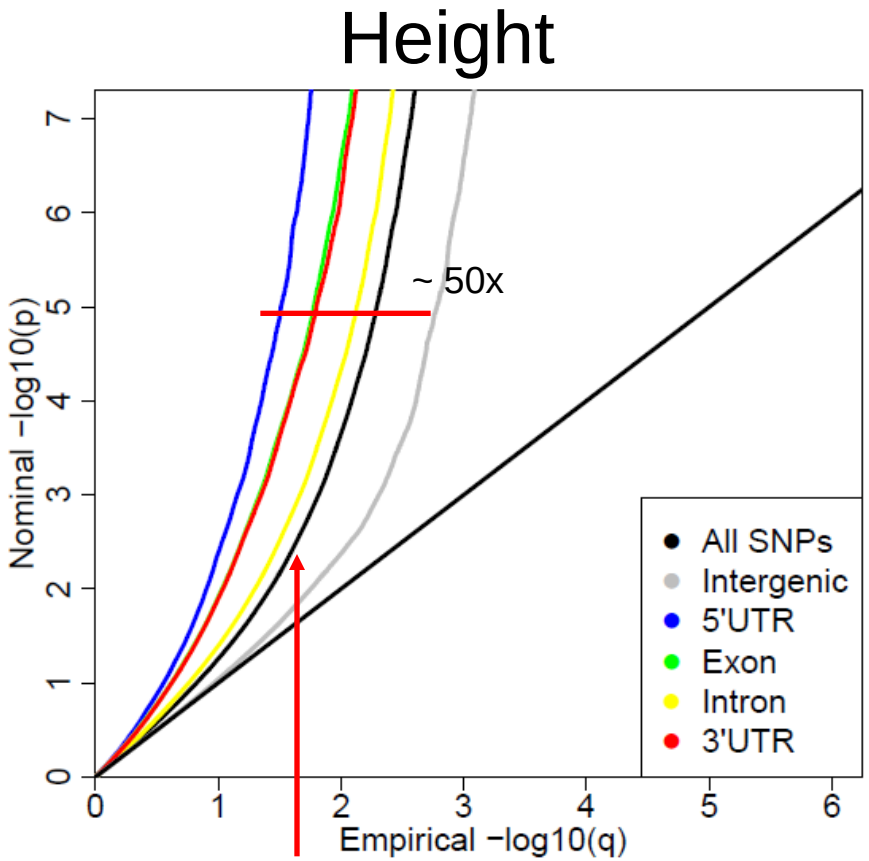
Functional genic elements

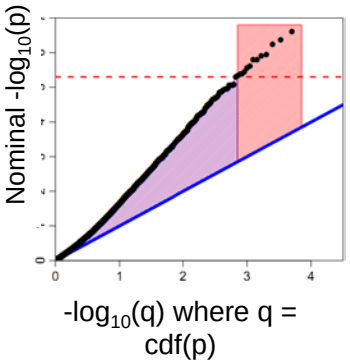
Exon = Coding
UTR = Regulatory
Intron = Neutral ?



Plumpton M and Barnes MR. *Bioinformatics for geneticists : a bioinformatics primer for the analysis of genetic data* 2007

I. Genomic annotation enrichment -



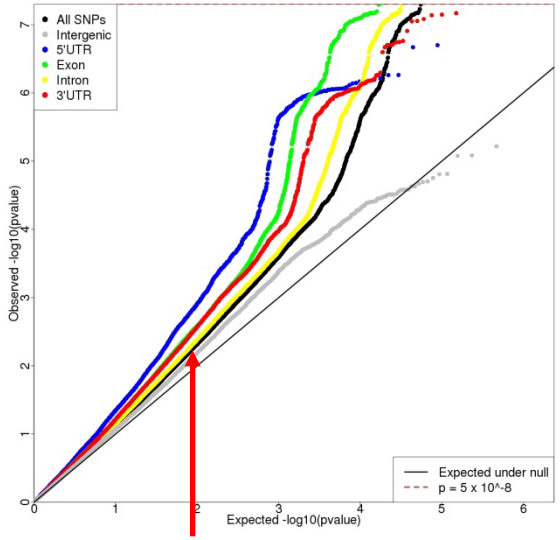


- Regulatory gene regions most enriched (5'UTR)
- Polygenic (1-2%)

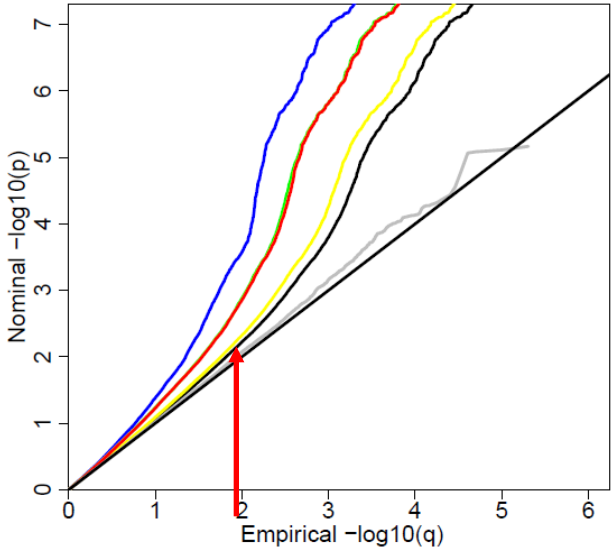
Schork et al. PLoS Genetics 2013

Complex disorders (psychiatry)

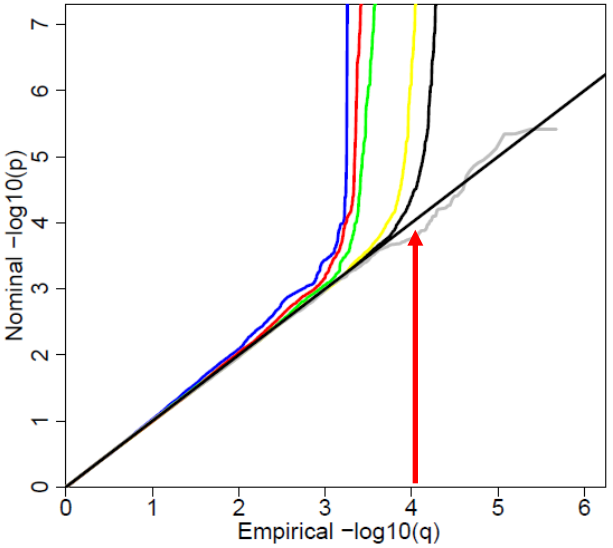
Bipolar disorder



Schizophrenia



Cigarettes Per Day



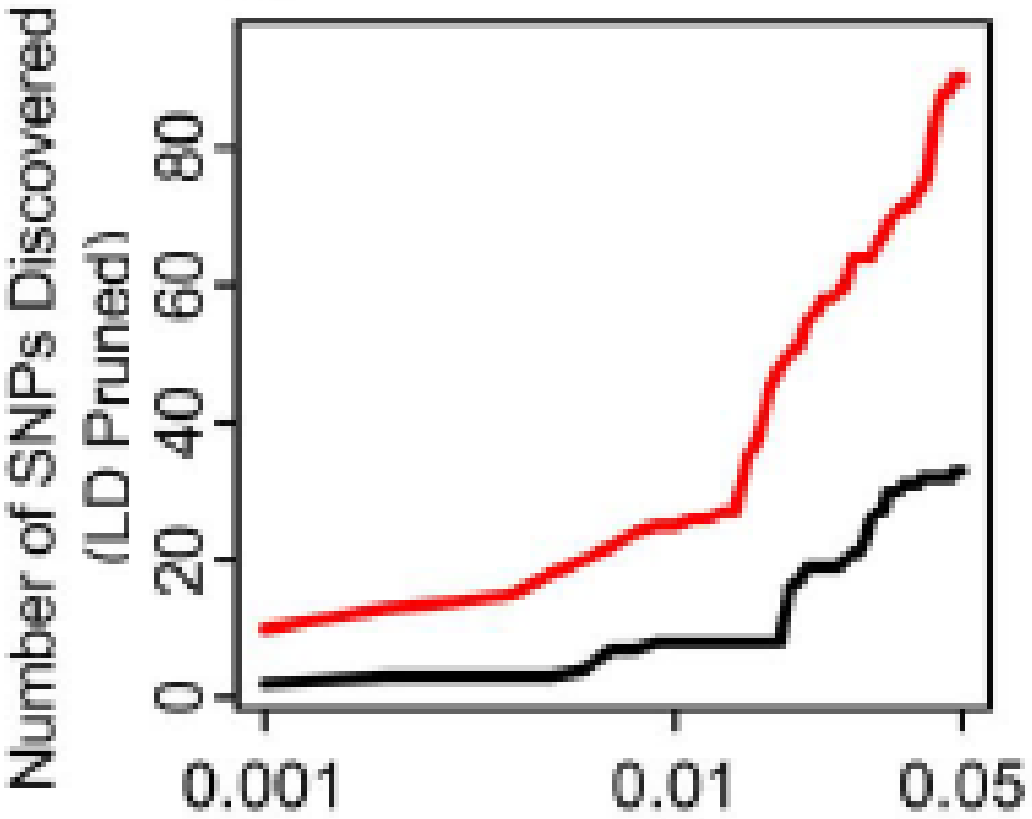
90 99 99.9 99.99

- 5’UTR
- Polygenic

Schork et al. PLoS Genetics 2013

Improved gene discovery

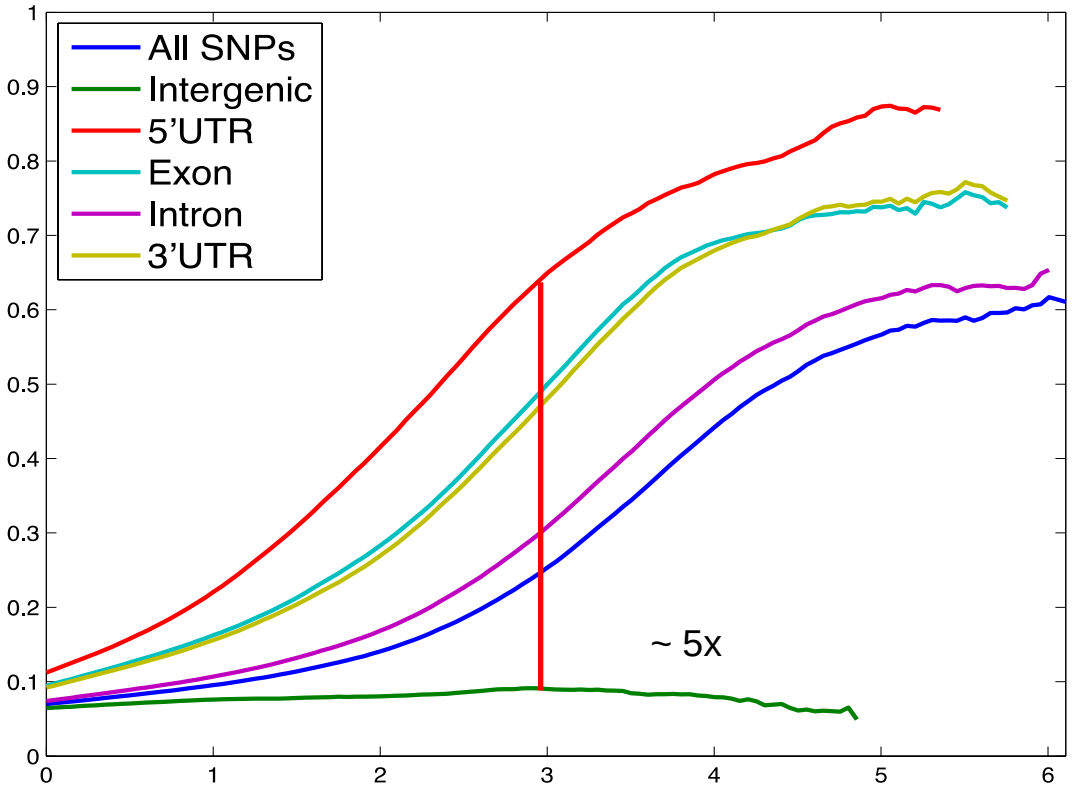
Schizophrenia



Schork et al. PLoS Genetics 2013

Vodoo statistics?

Replication rate Schizophrenia sub-studies



Andreassen et al. Schizophr Bull 2014

Outline

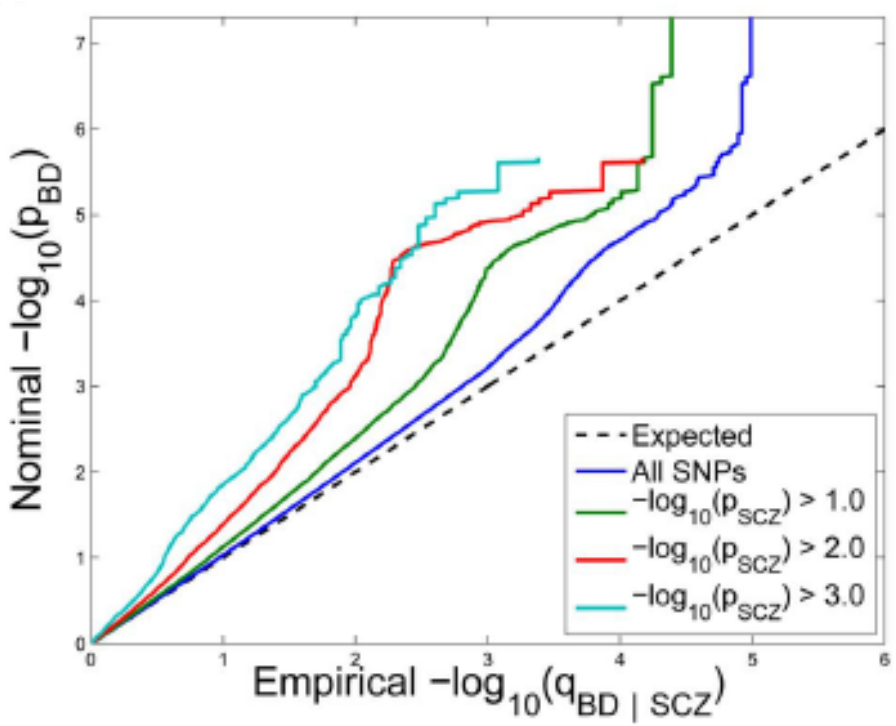
I. Genomic annotation enrichment
II. Pleiotropy enrichment
III. Increased discovery & replication
IV. Improved prediction

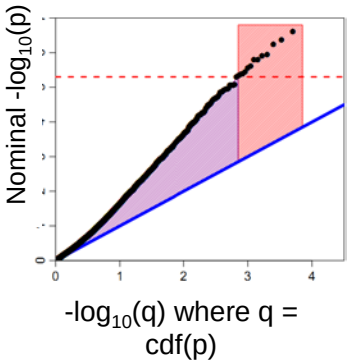
II. Pleiotropy enrichment

- 22 000 genes, millions of traits/diseases: Some genes must affect several traits
- Utility:
  - *Gene discovery – conditional FDR*
  - *Mechanisms – choosing phenotypes*

Schizophrenia (SCZ) associations enrich signal in bipolar disorder (BD)

Conditional Q-Q plots



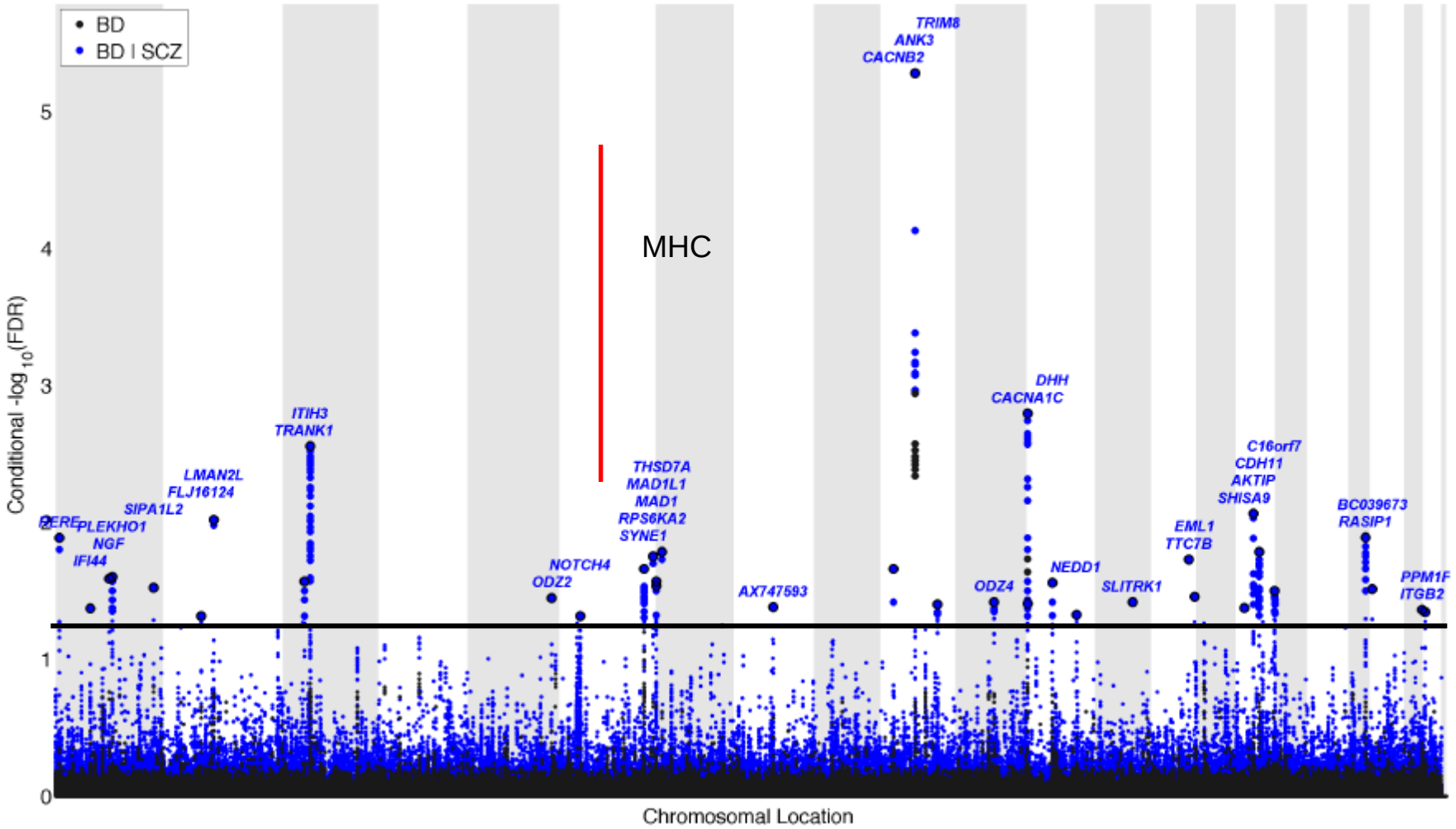


- Samples: PGC SCZ1, BIP1 no overlap
- Shared SNPs (1.2%)

Andreassen et al. PLoS Genetics 2013.

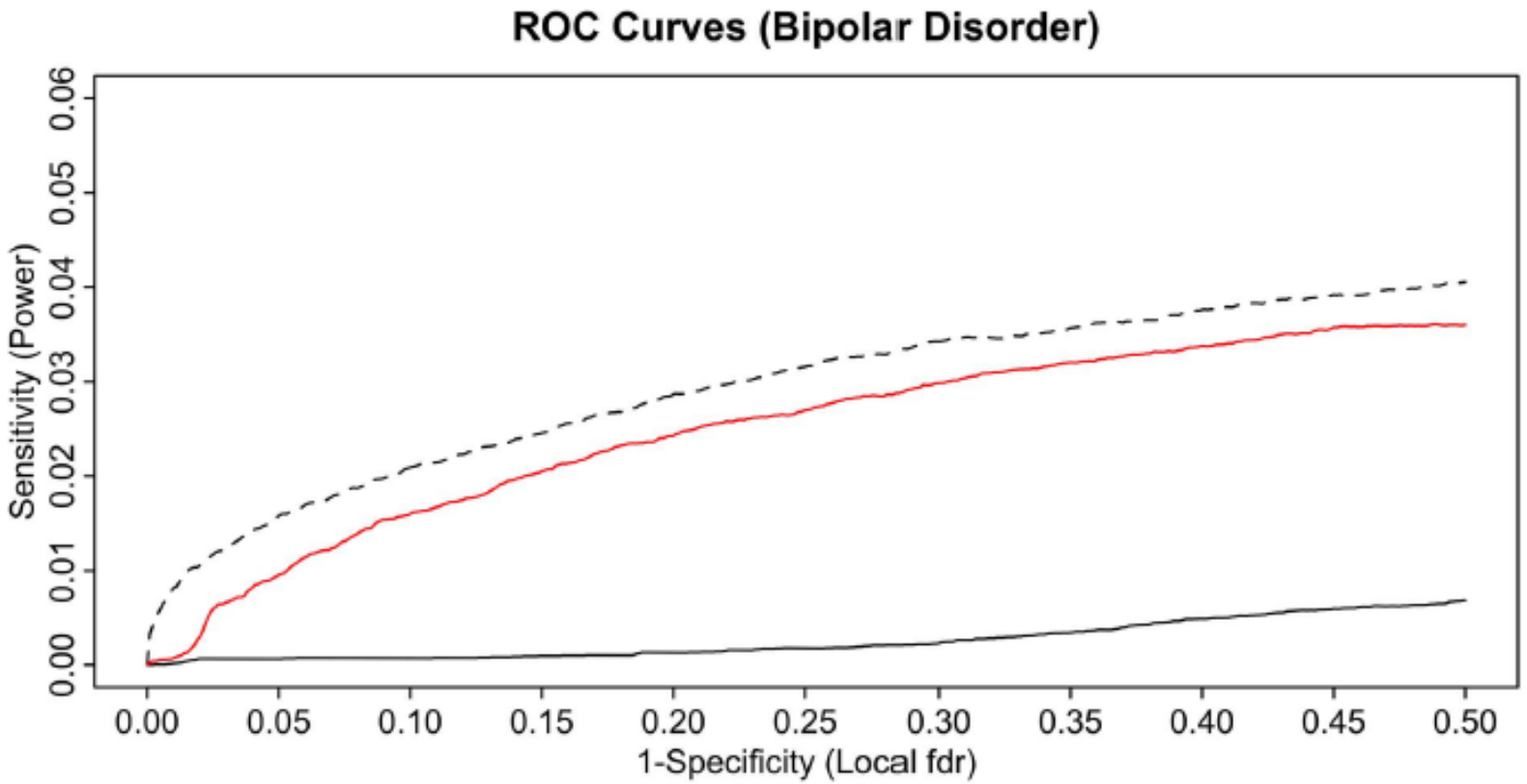
Improved gene discovery BD

35 vs 5 loci



Andreassen et al. PLoS Genetics 2013.

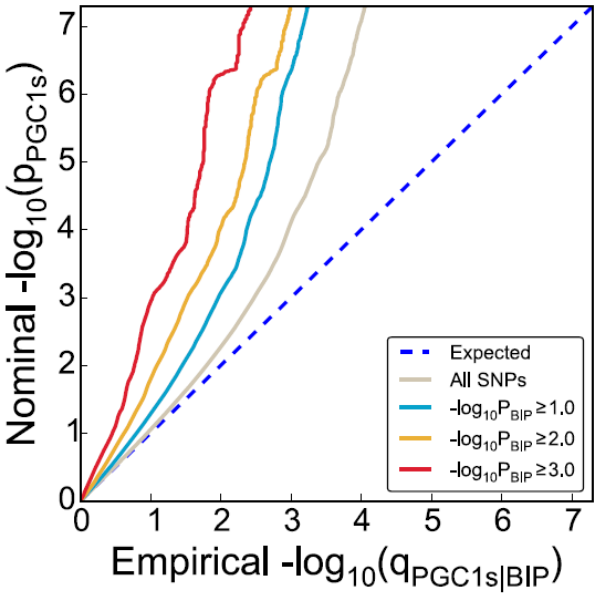
Improved sensitivity same specificity



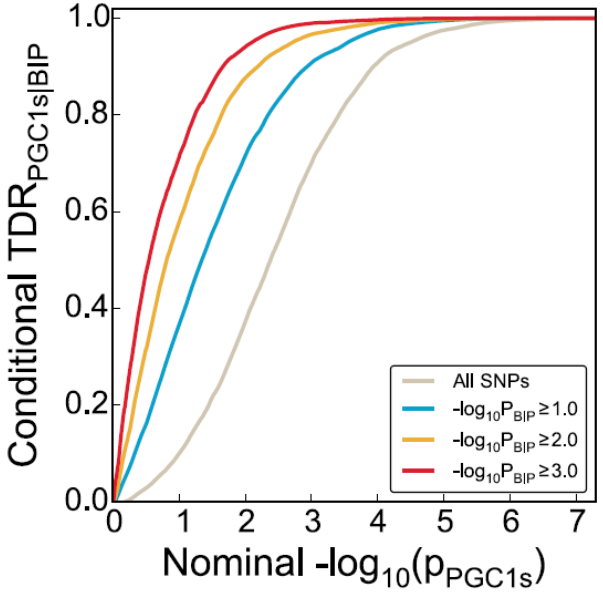
Andreassen et al. PLoS Genetics 2013.

BIP increases association SCZ (larger sample)

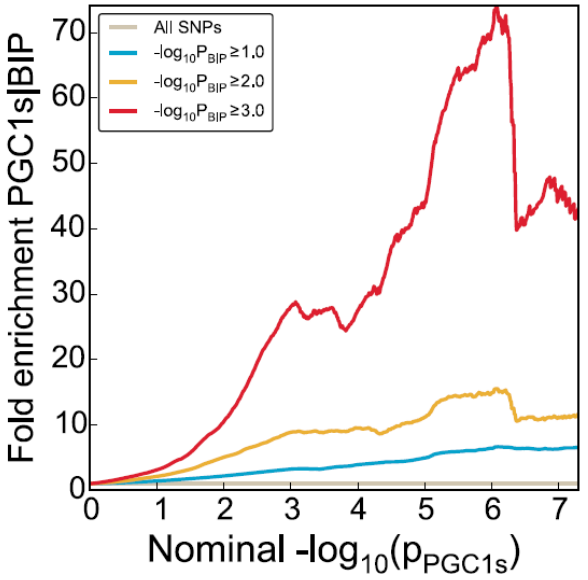
Q-Q

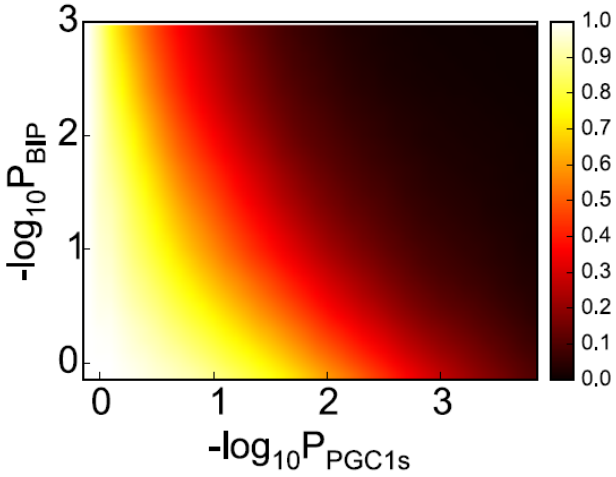


TDR



Fold-enrichment





Wang et al. In prep

Pleiotropy to understand disease mechanisms

Schizophrenia GWAS

- Schizophrenia (SCZ, PGC1 n=21 000)

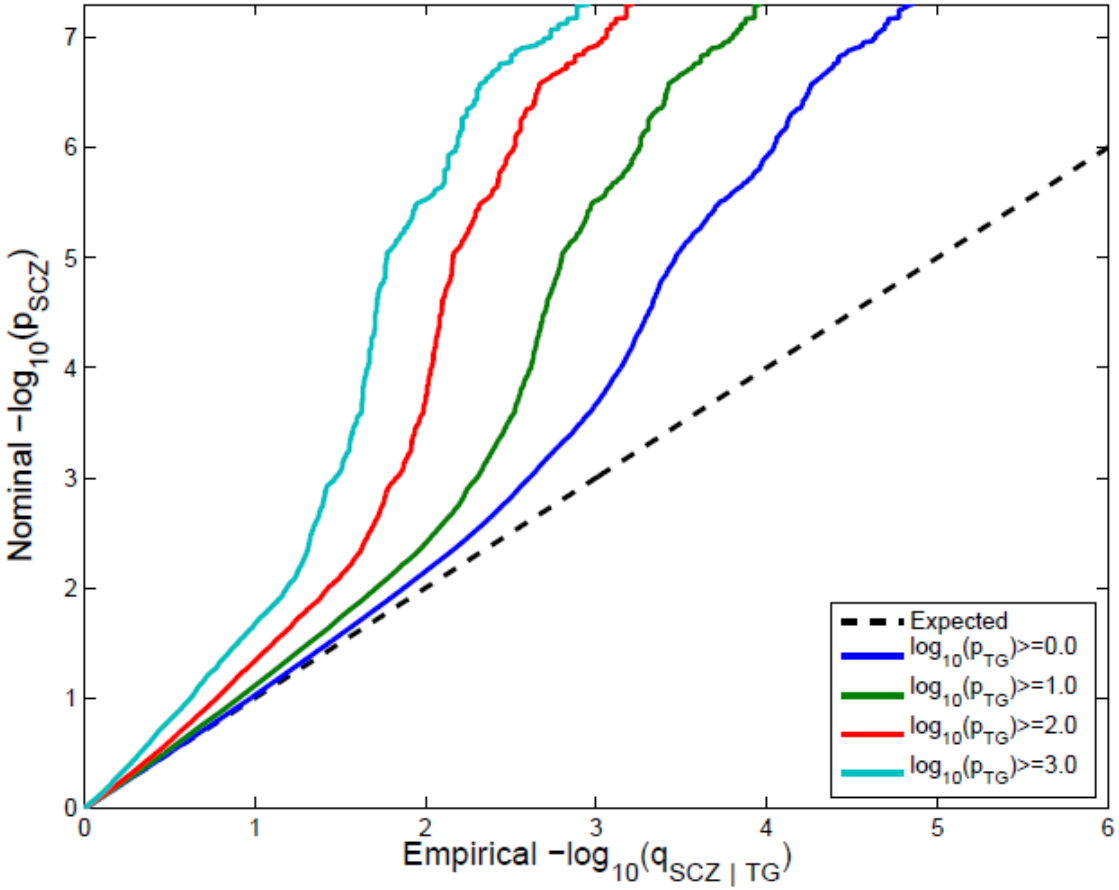
Cardiovascular disease (CVD) risk factors GWAS

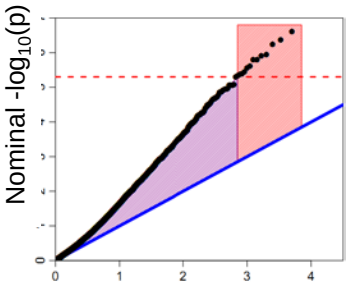
- Systolic Blood pressure (SBP, n=203 000)
- Dyslipidemia (LDL, HDL, TG, n=96 000)
- Body Mass Index (BMI, n=123 000)
- Waist Hip Ratio (WHR, n=77 000)
- Diabetes (T2D, n=22 000)

Andreassen et al. AJHG 2013

Blood lipid associations enrich SCZ signal

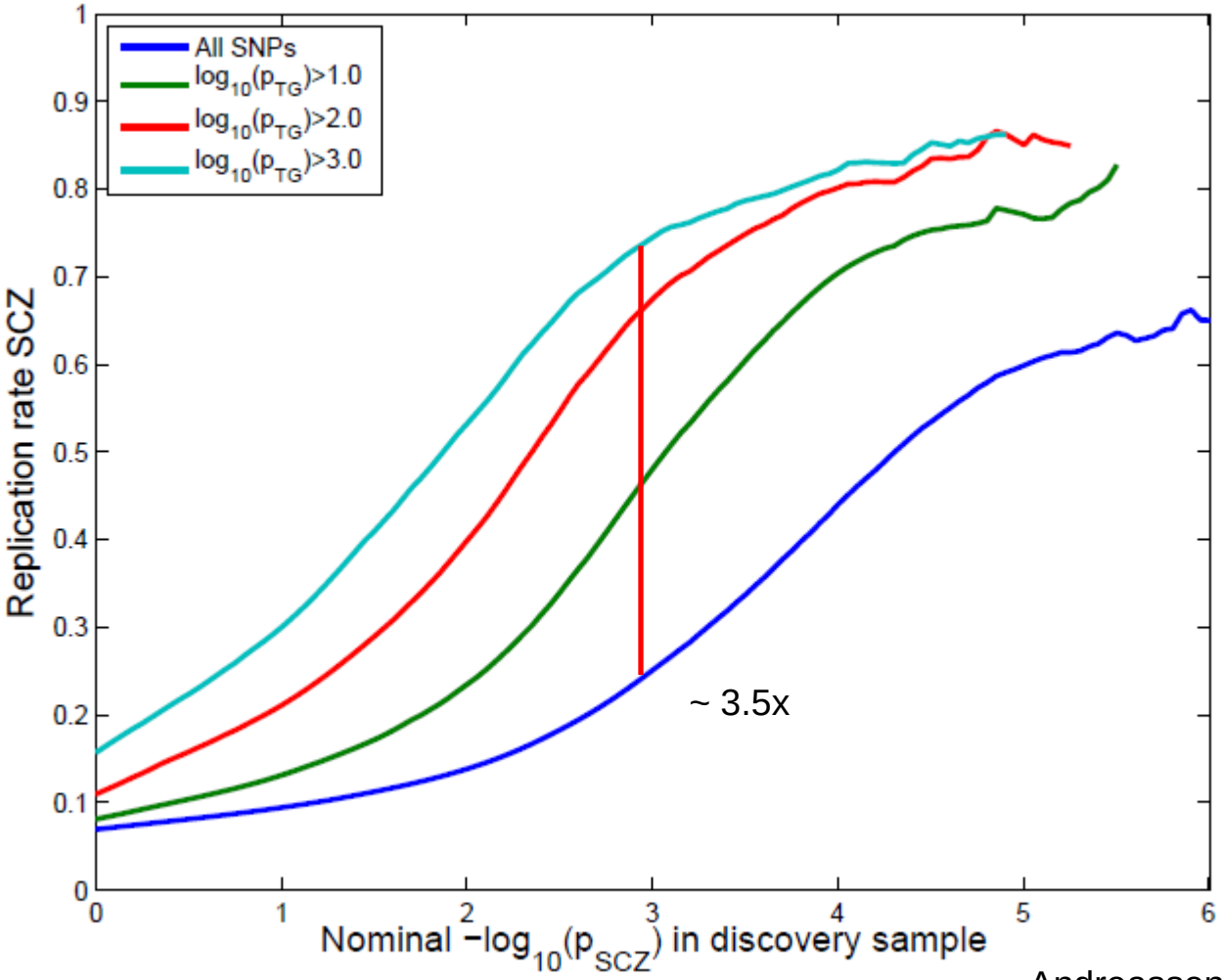
Triglycerides (TG)





Andreassen et al. AJHG 2013

Replication rate (SCZ-TG)



Andreassen et al. AJHG 2013

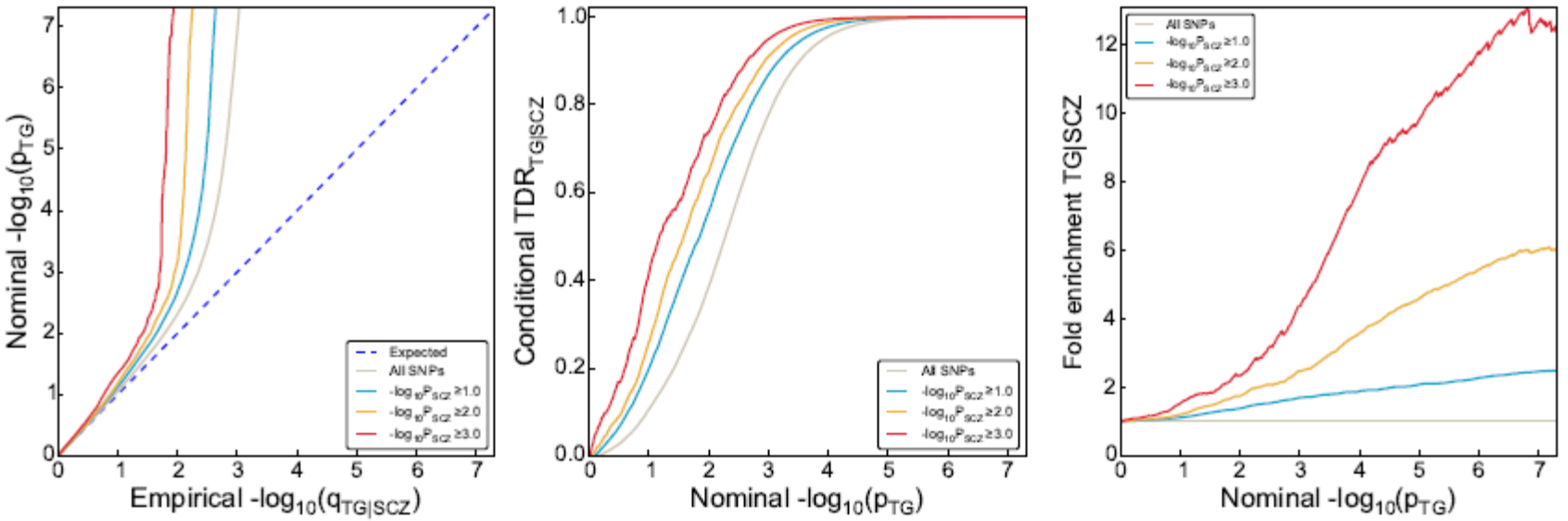
Common biology SCZ & CVD?

- Most overlap in dyslipidemia; TG, LDL, HDL
- Some overlap BMI, SBP, WHR
- No overlap T2D

Suggests lipid biology as mechanism

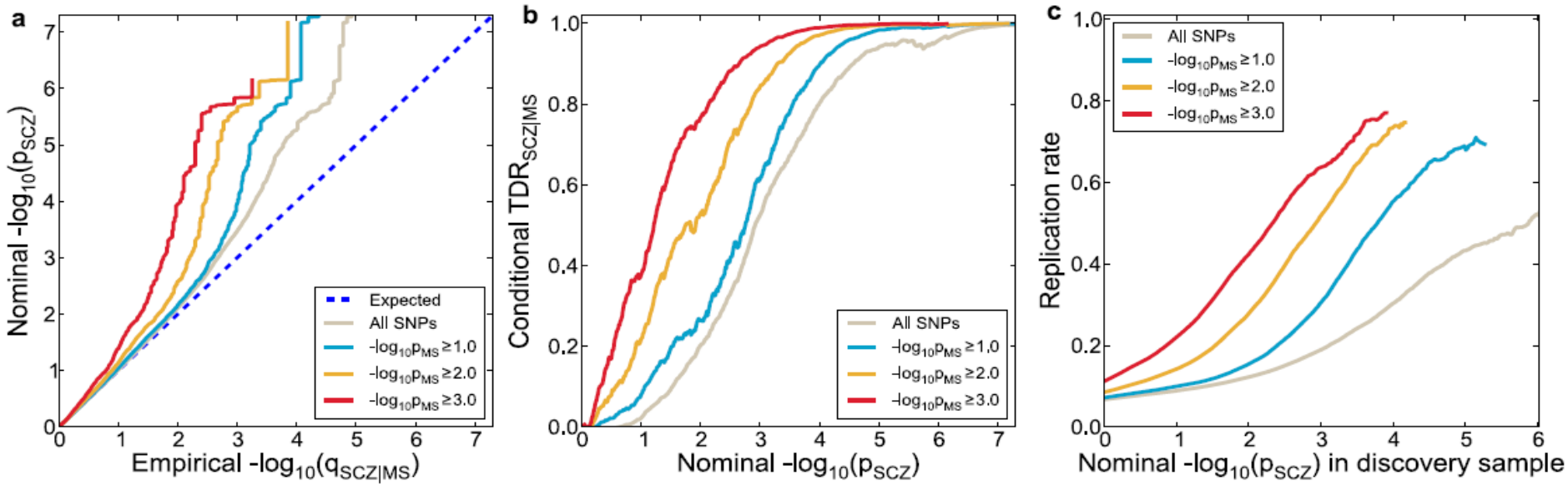
Andreassen et al. AJHG 2013

Triglycerides (TG) – SCZ
(larger sample, n=188 000)



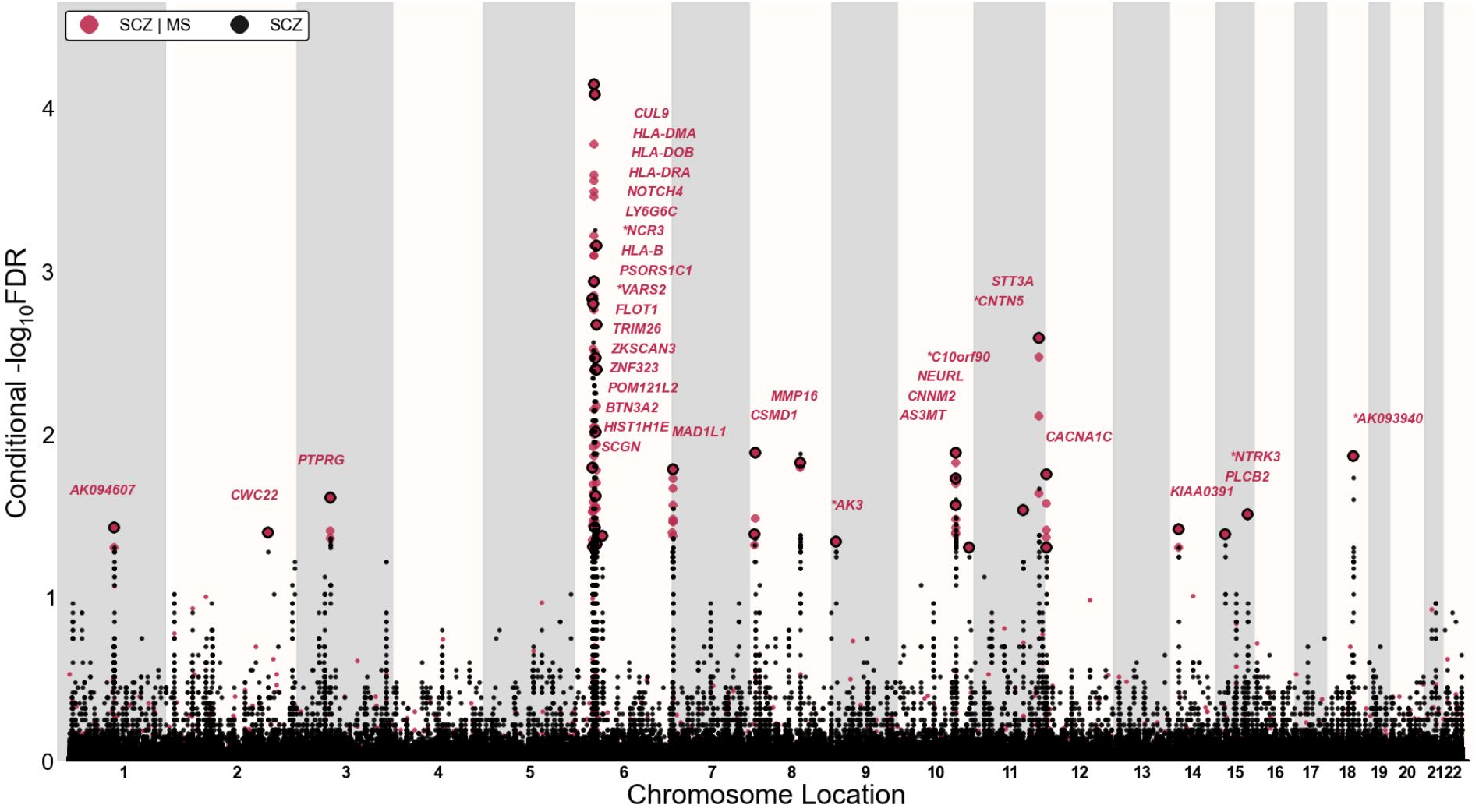
Immune-mediated diseases and SCZ

Multiple sclerosis and SCZ



Andreassen et al. 2014

SCZ conditioned on MS

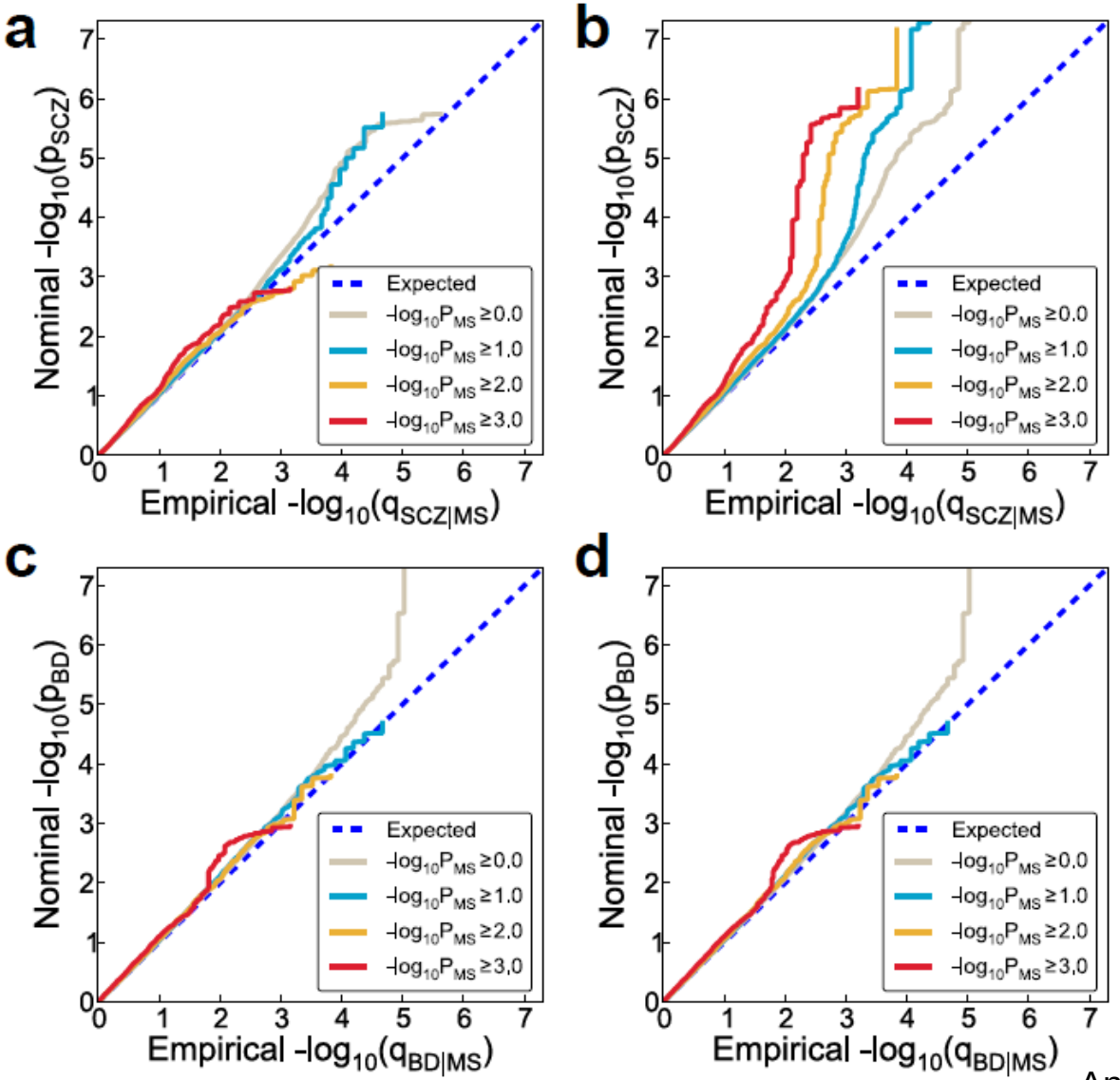


Andreassen et al. 2014

MHC, Bipolar disorder

SCZ

BIP

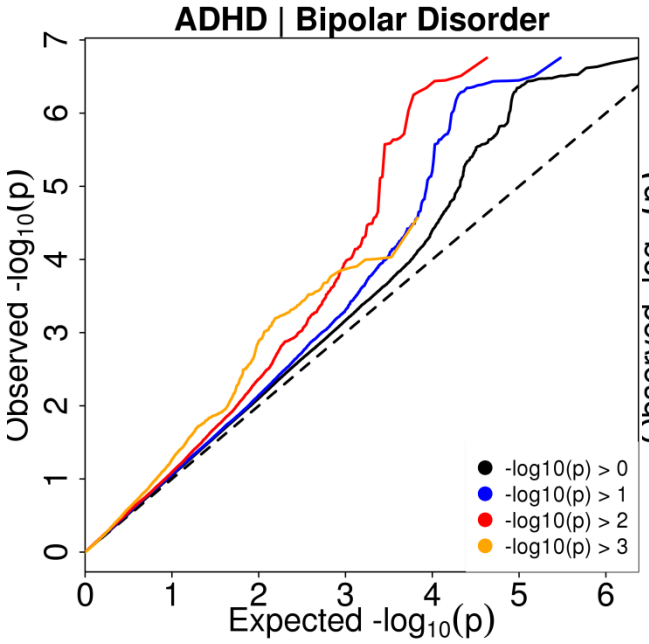


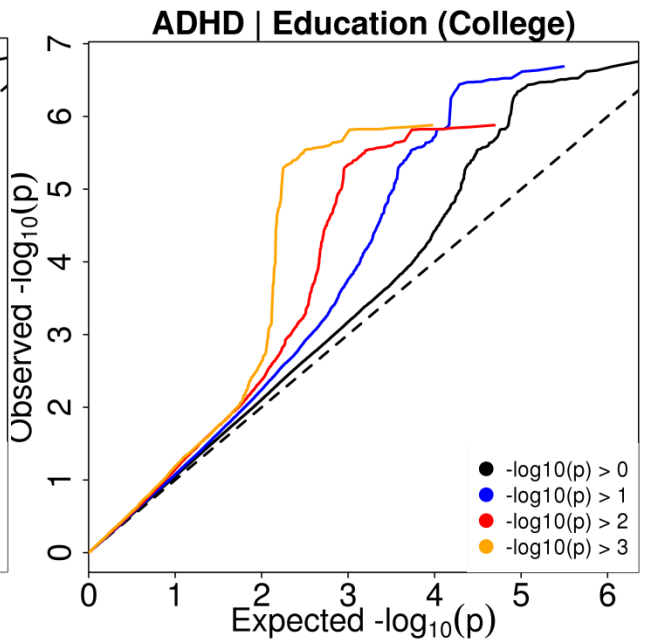
Andreassen et al. 2014

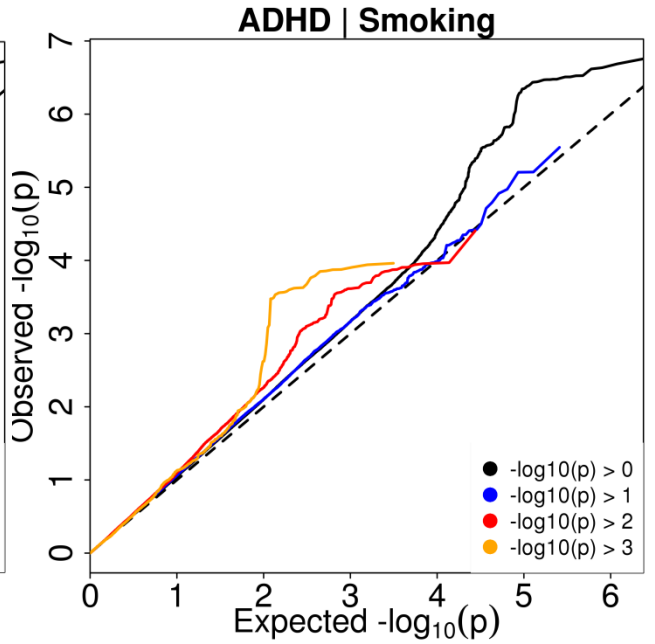
ADHD ‘Pleiotropy’

- ADHD comorbidity
- psychiatric and behavioral phenotypes:

  bipolar disorder, education and smoking







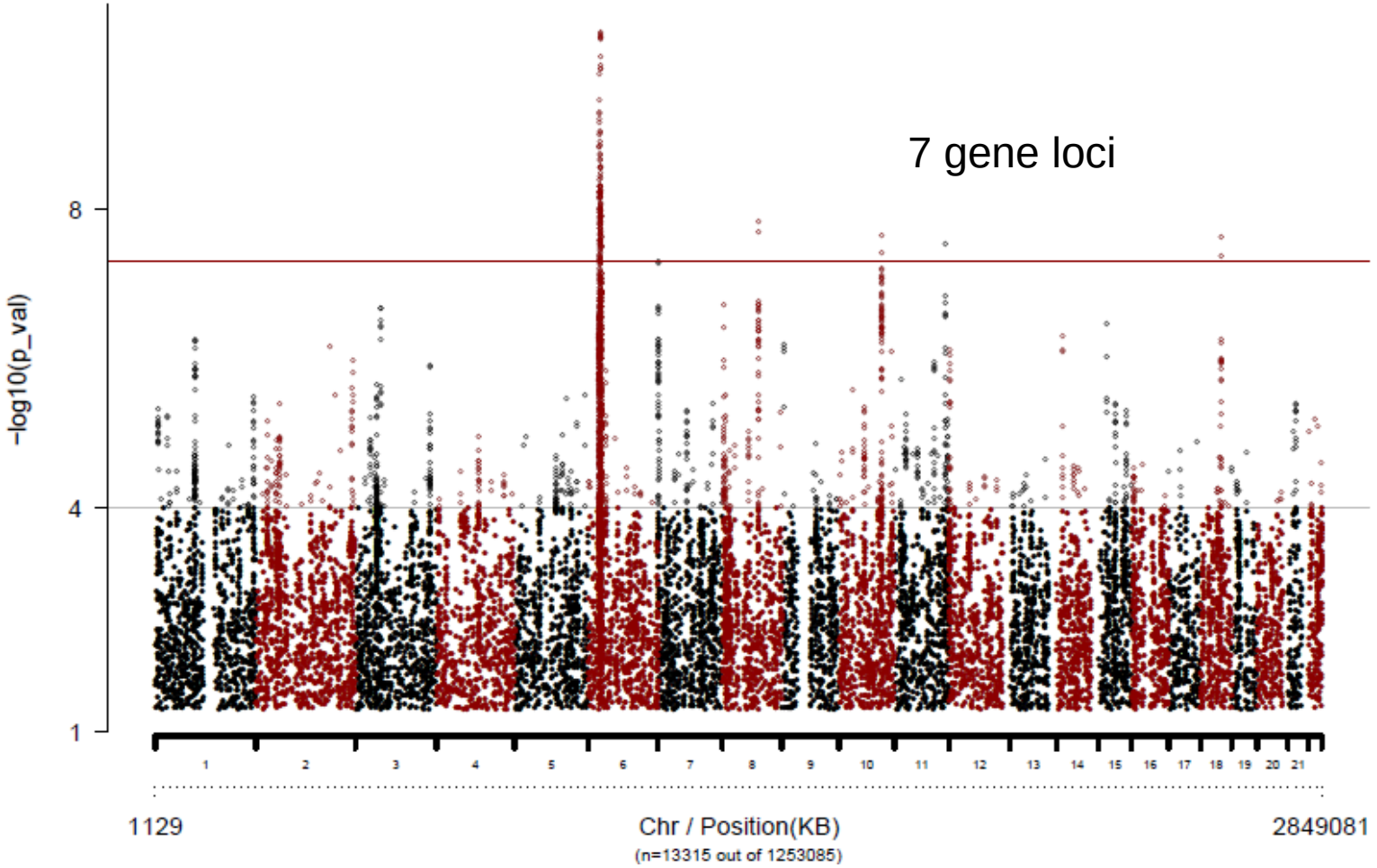
Schork et al. In prep

Outline

I. Genomic annotation enrichment
II. Pleiotropy enrichment
III. Increased discovery & replication
IV. Improved prediction

Standard GWAS

PGC – SCZ1; 8,832 cases 12,067 controls



PGC Schizophrenia Work Group. Nat Genet 2011

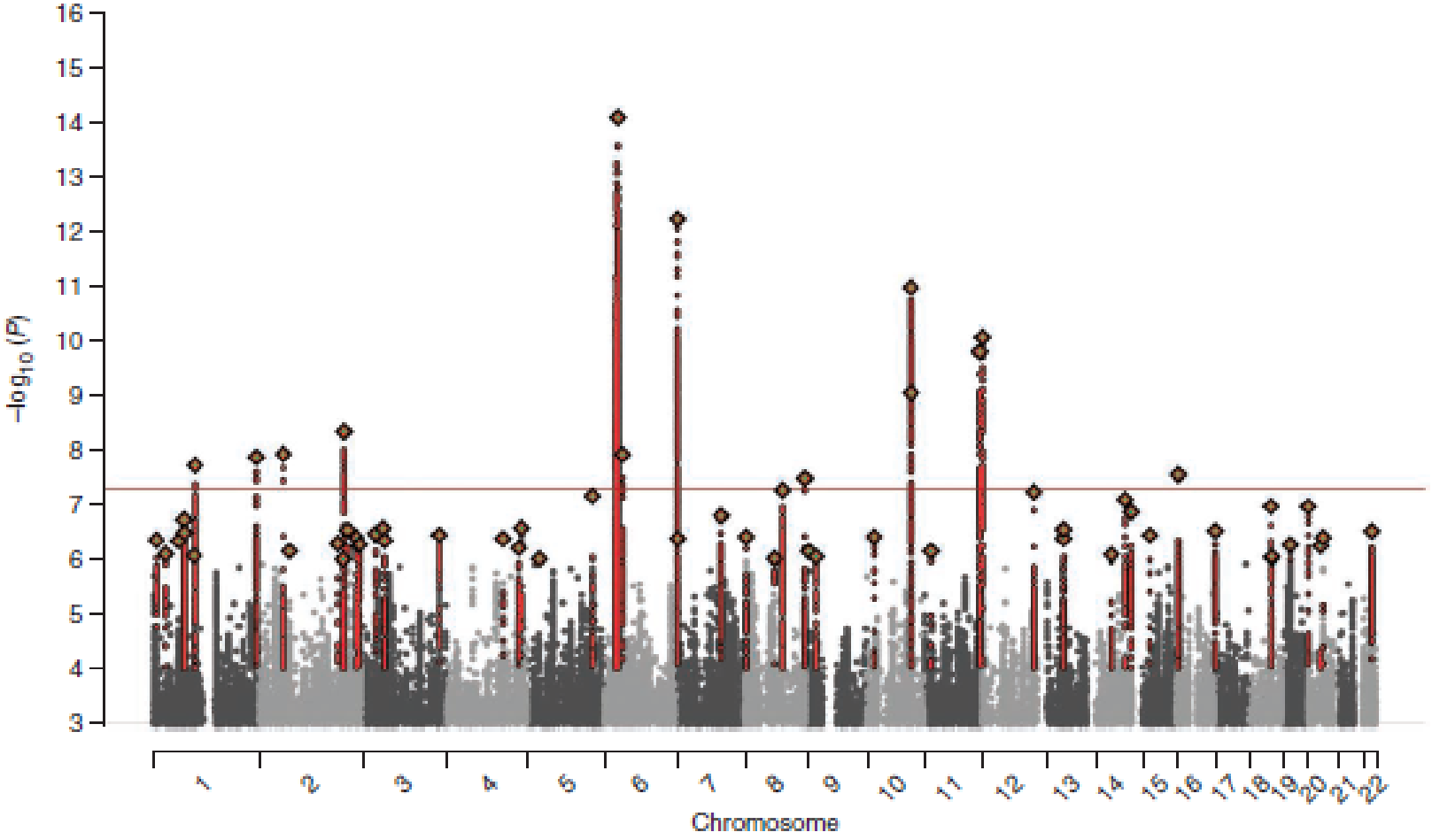
Standard GWAS

PGC SCZ1 + Sweden

Ripke et al. Nat Genet 2013

- Sweden SCZ (5,001 cases 6,243 controls)
- PGC1 SCZ (8,832 cases 12,067 controls)
- Total n=13,833 + 18,310 = 32,143

12 SCZ gene loci



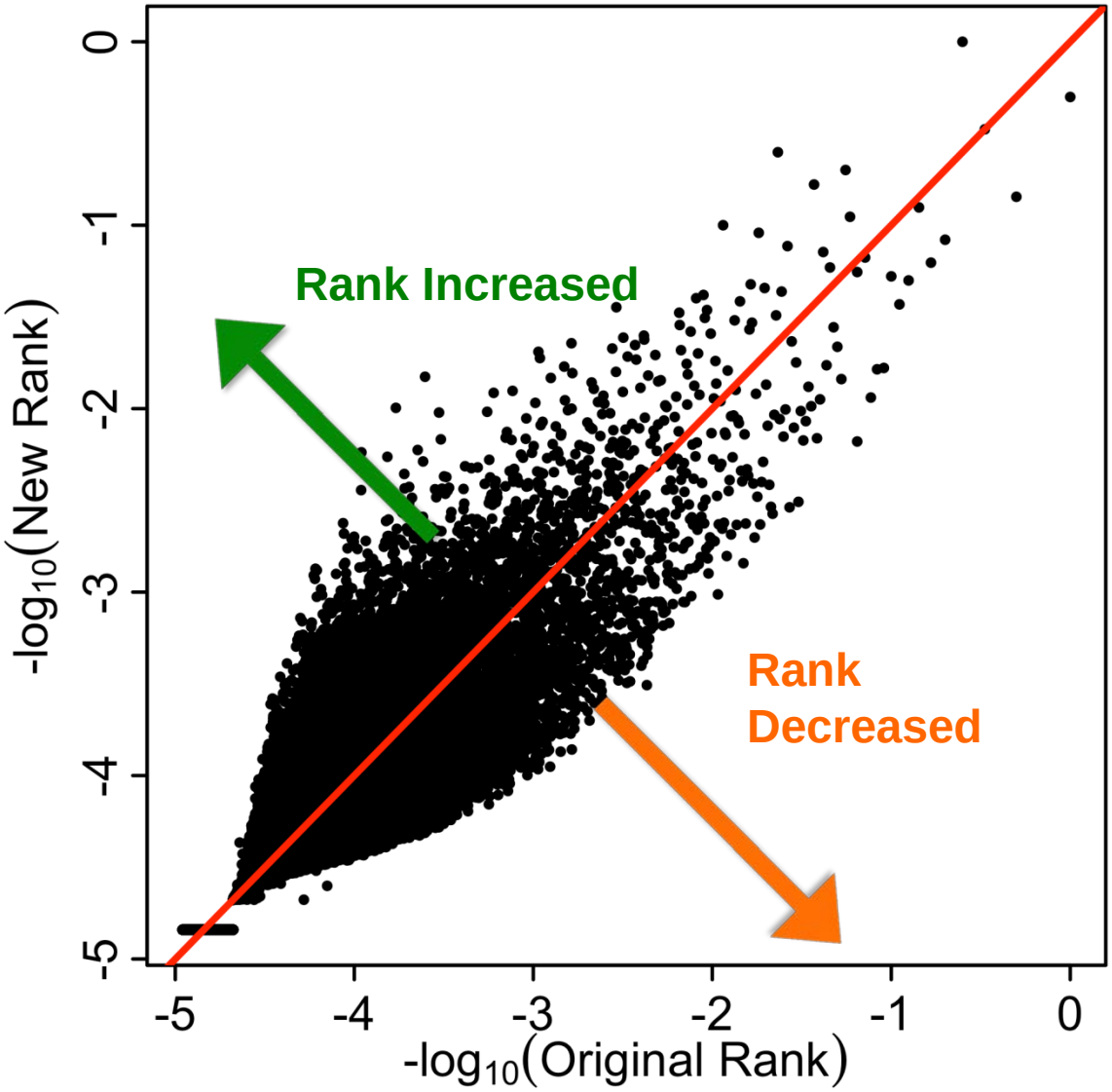
Ripke et al 2013

New statistical tools

- Bayesian approach, use all priors
  - Enrichment exon, 3'UTR, 5'UTR, assoc phenotype
- The covariate modulated false discovery rate (CM^3) (developed from Zablocki et al 2014)
- SCZ: PGC SCZ1 + Sweden sample
  - Boosting sample: PGC BIP1 sample – remove overlap

Wang et al. In prep

Re-ranking SNPs



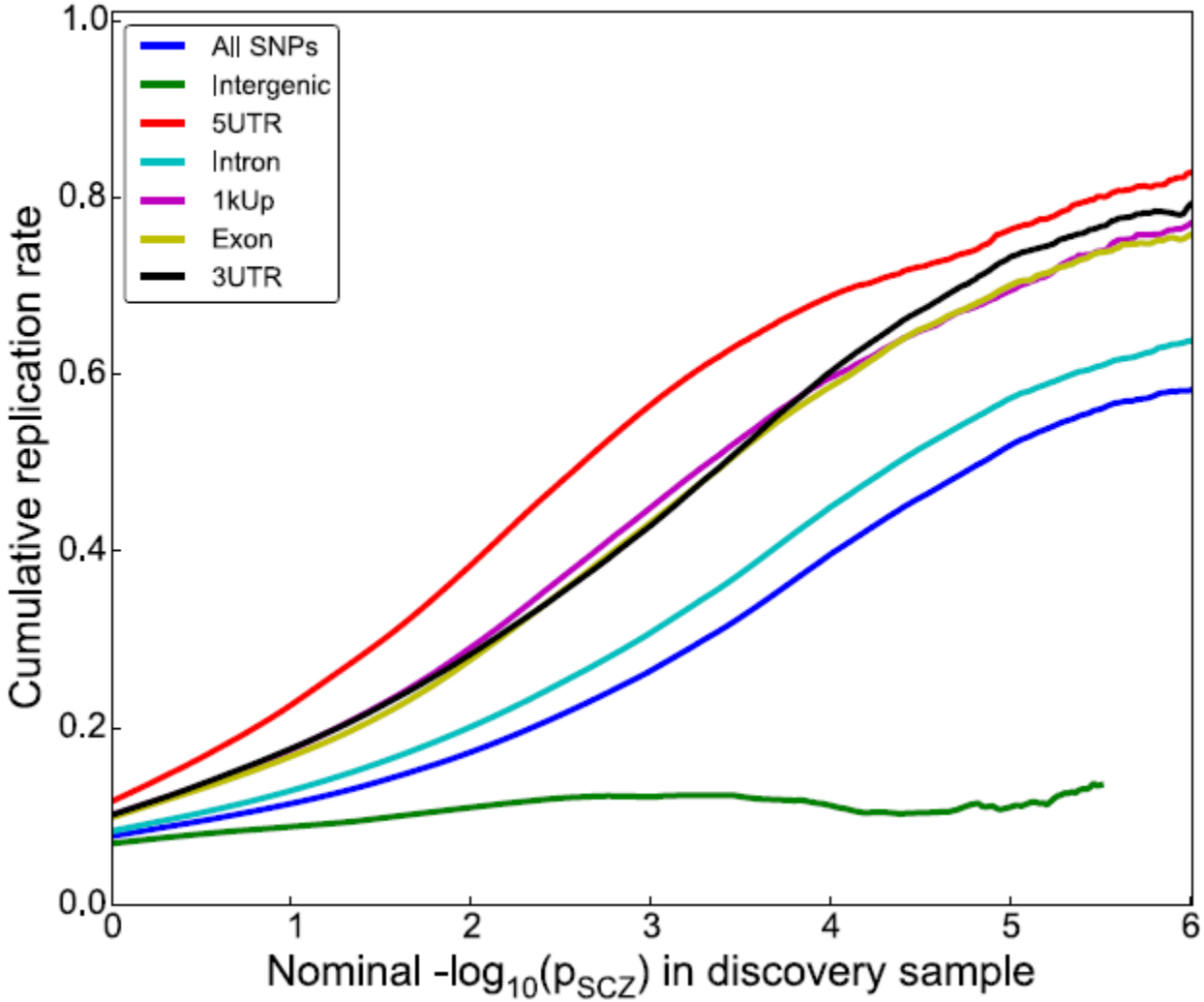
Zablocki et al. In review

New stats SCZ discovery

- 105 SCZ gene loci (cmFDR < 0.05)
- pruned LD r^2 < 0.1 and 1M distance

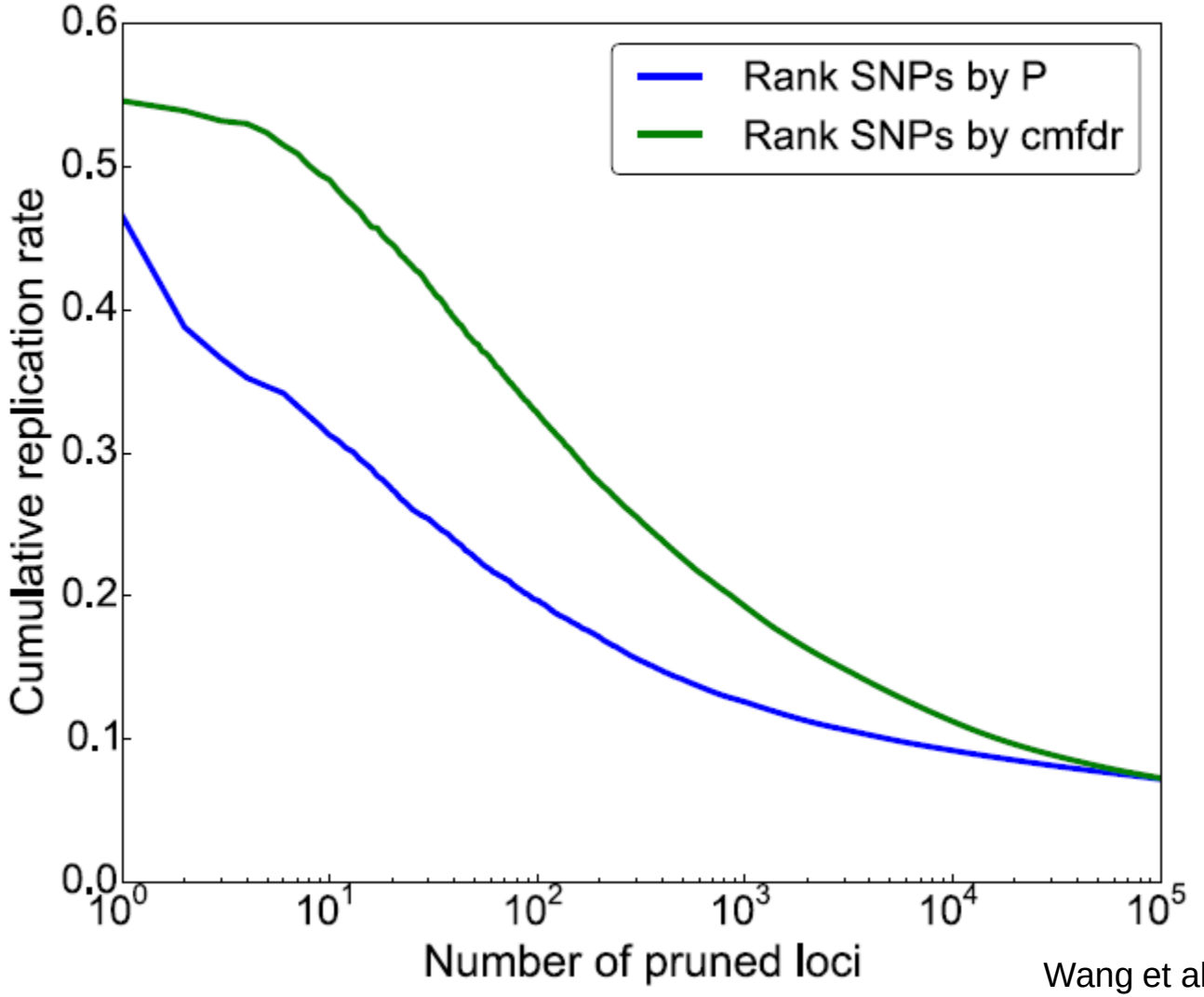
Wang et al in prep

Replication rate - annotation categories



Wang et al. In prep

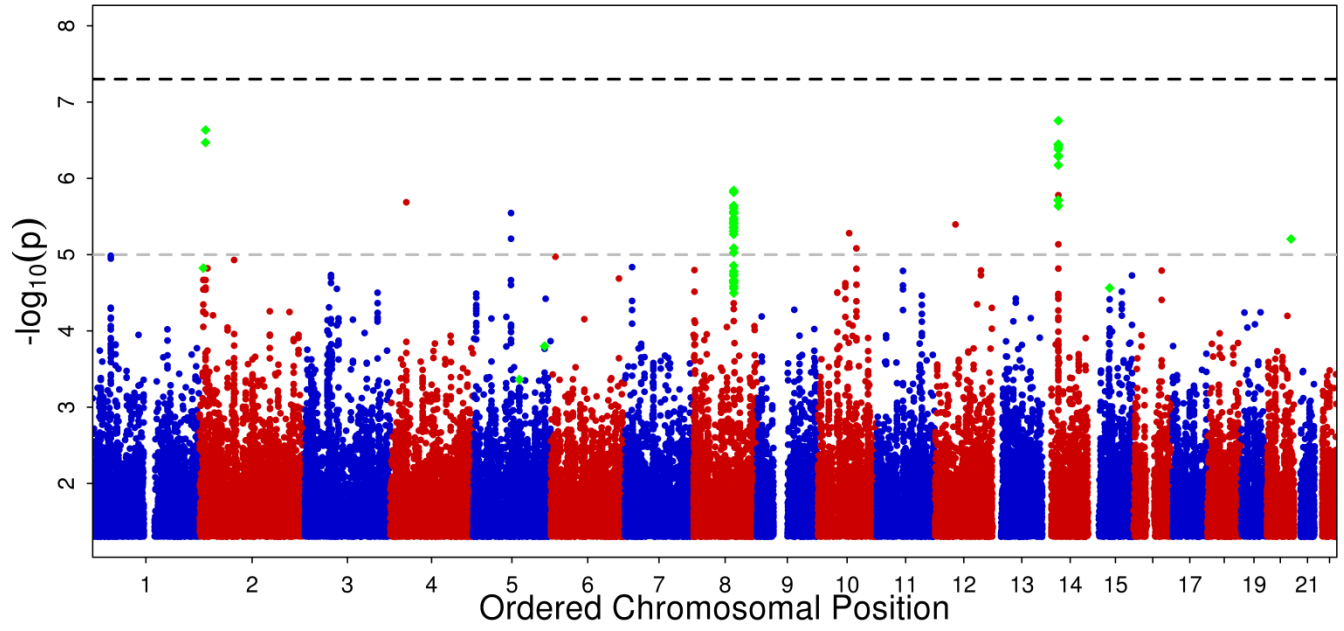
Replication rate
CM3 vs Standard GWAS

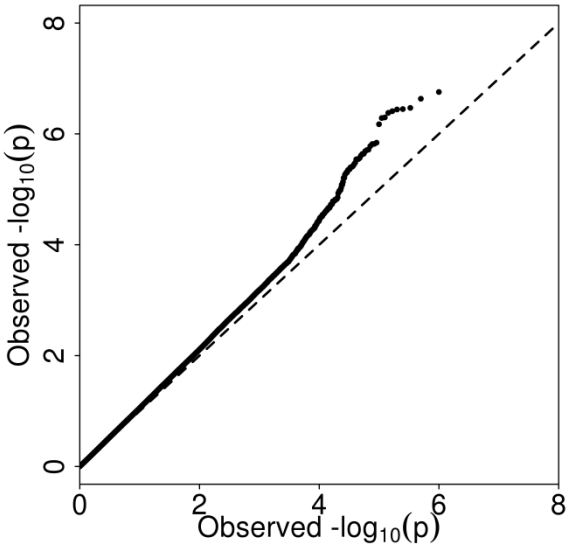


Wang et al. In prep

ADHD

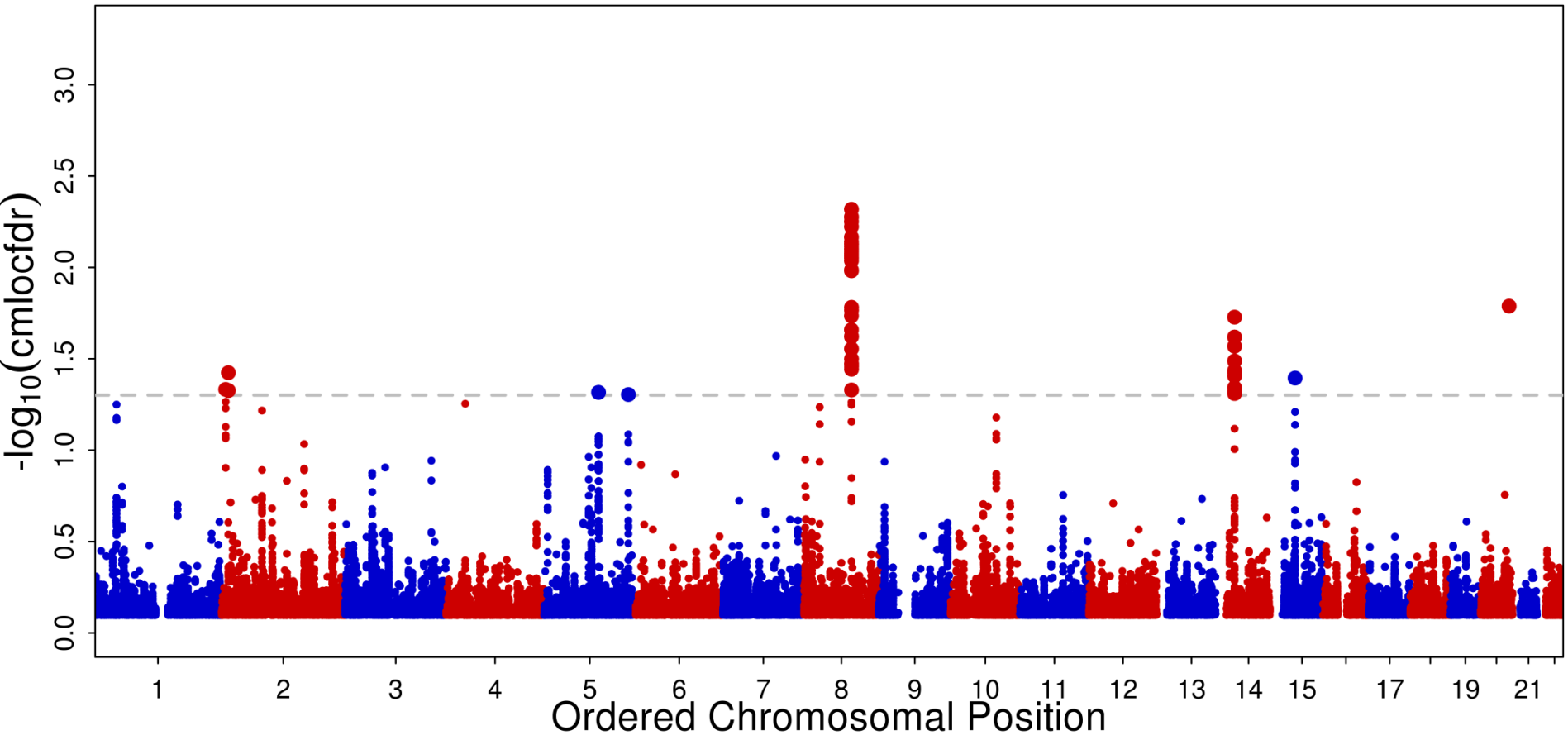
- PGC ADHD1 GWAS provided no genome-wide significant loci (Neal et al 2011)





ADHD CM3

Covariate modulated local FDR



Schork et al. In prep

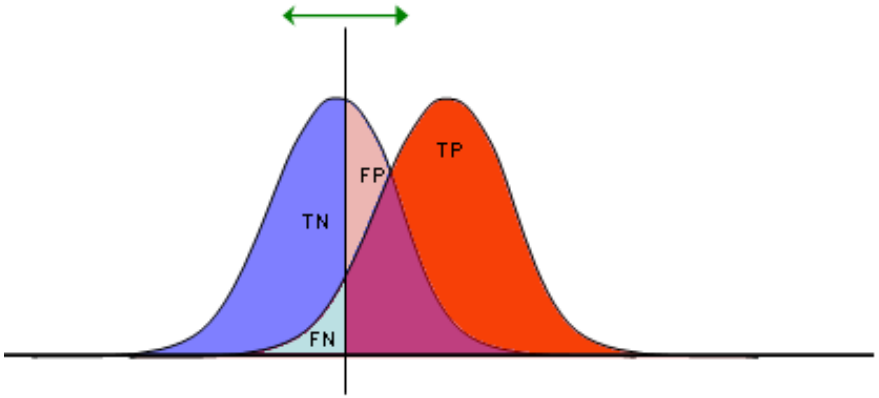
Outline

I. Genomic annotation enrichment
II. Pleiotropy enrichment
III. Increased discovery & replication
IV. Improved prediction

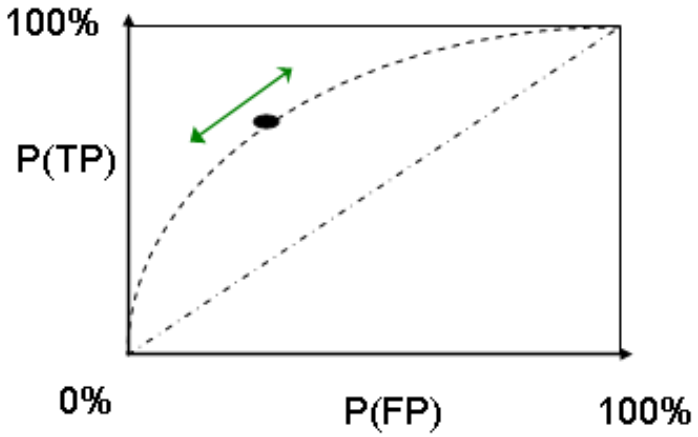
IV. Prediction

- Explained variance (Nagelkerke R^2) may depend on sample size and case/control ratio
- Receiver Operator Characteristics (ROC) – standard for estimating prediction

Prediction – ROC
(sensitivity, specificity)



TP	FP
FN	TN
1	1



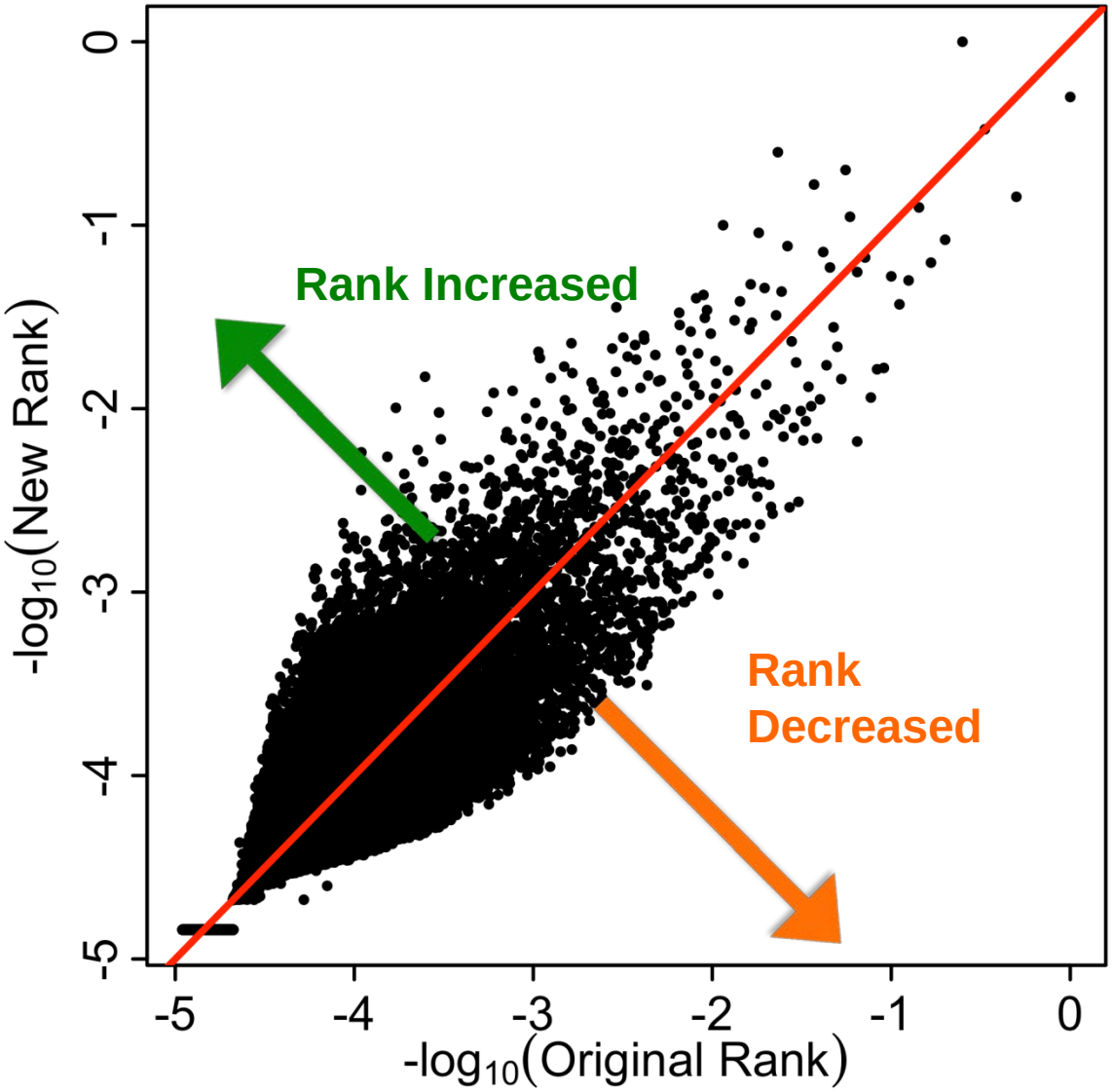
SCZ prediction

- Training set
  - PGC SCZ1 + Sweden (not TOP8)
- Test set
  - TOP8 (n=350 cases, 350 controls)
- Method: covariate modulated fdr (CM3)

  re-rank SNPs based on priors:
  - annotation categories (5'UTR, 3'UTR, exons)
  - PGC BIP1 (removed overlap)
- Compare with standard log OR method (Purcell et al)

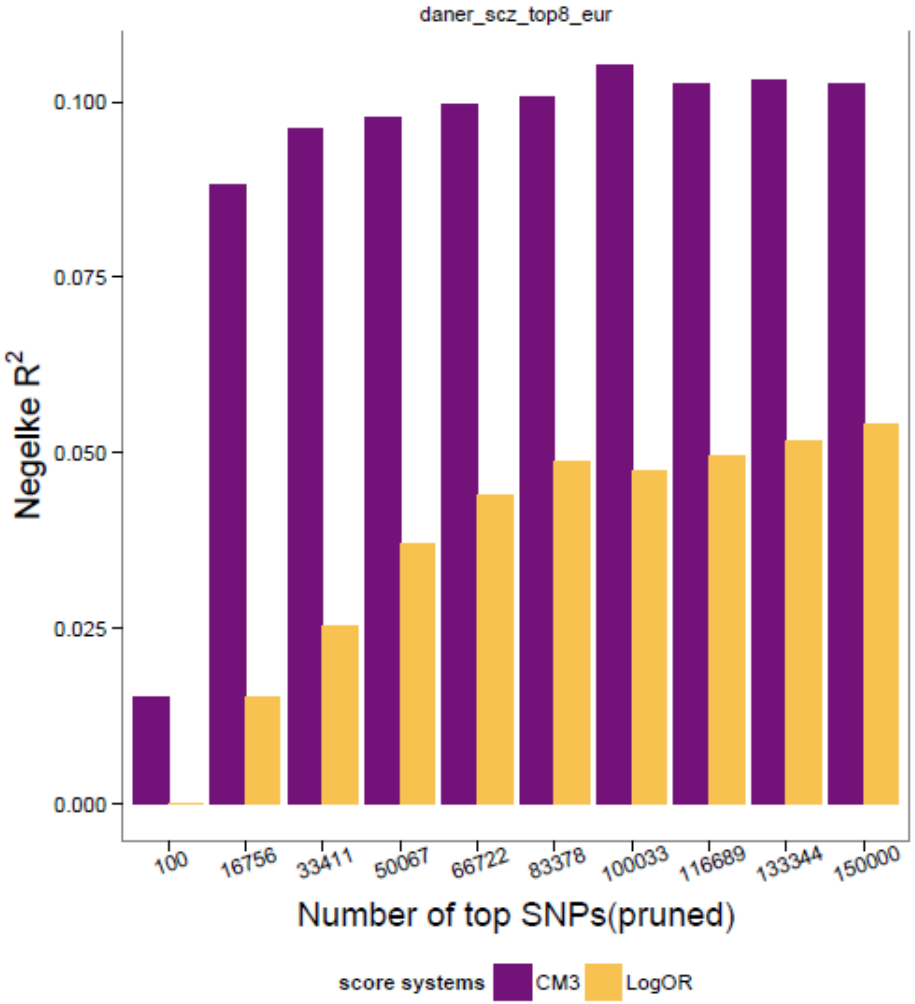
Wang et al. In prep

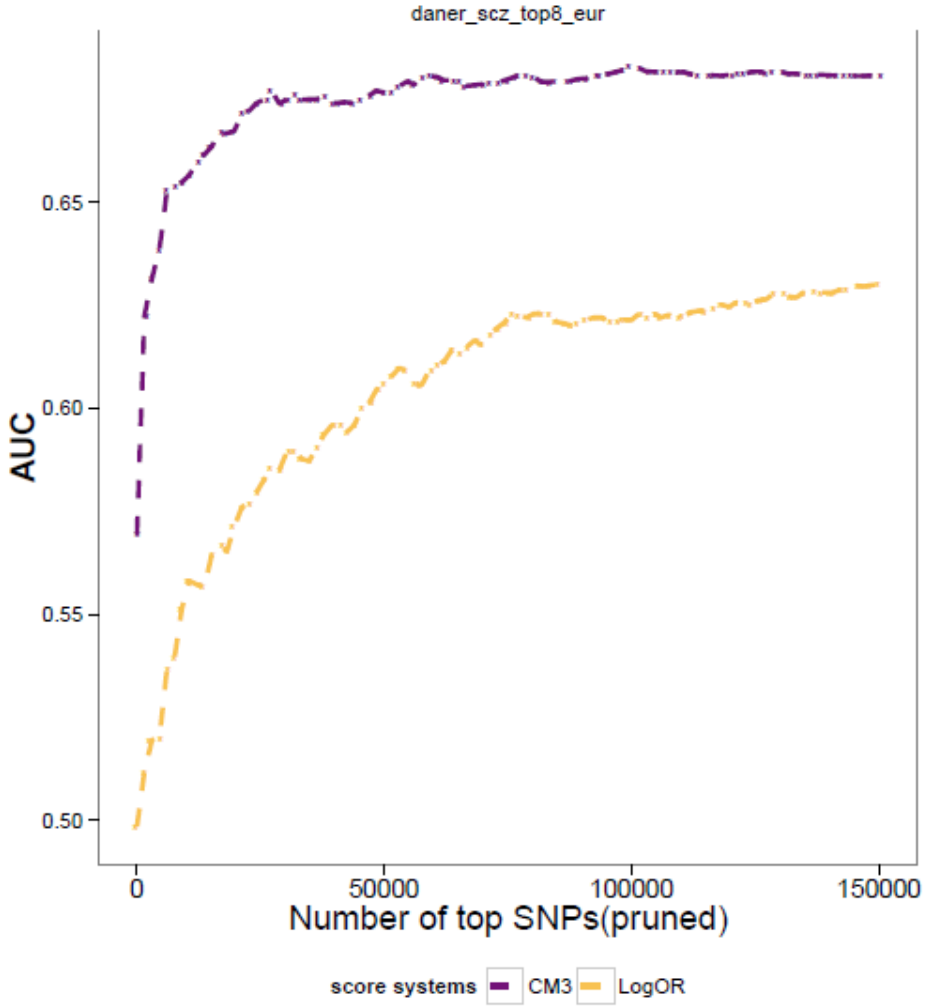
Re-ranking SNPs



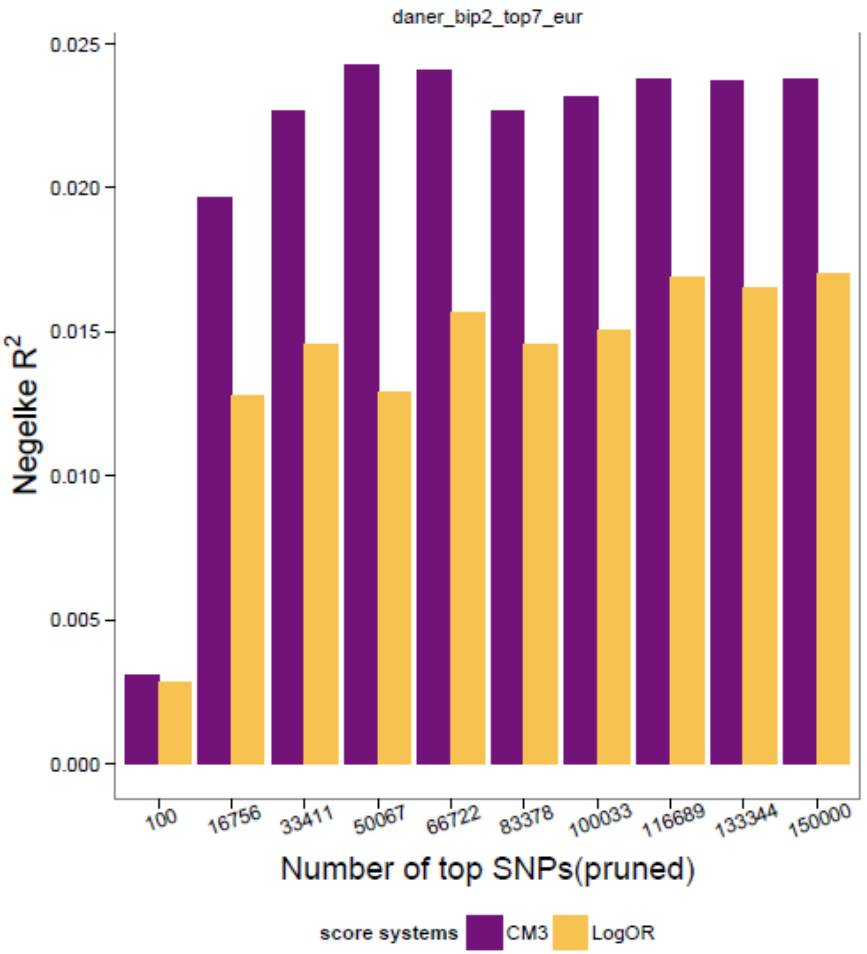
Zablocki et al. In review

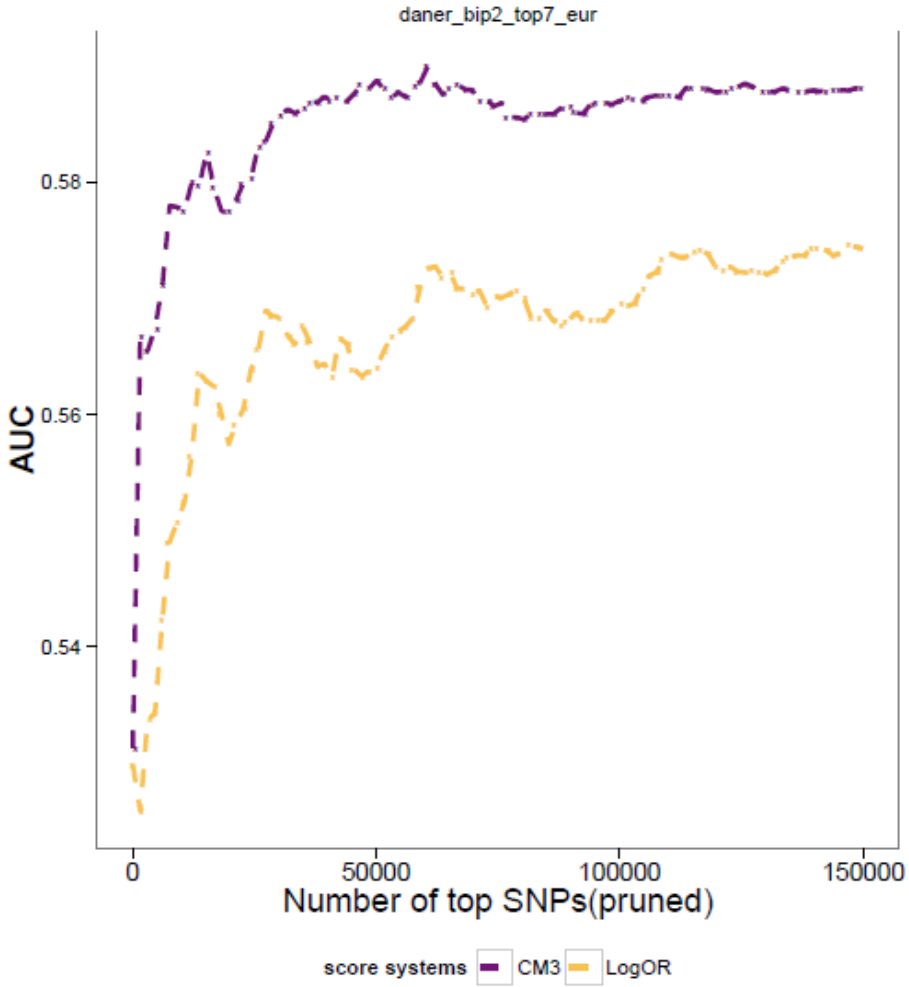
SCZ


daner_scz_top8_eur
0.100
0.075
0.050
0.025
0.000
Negelke R^2
100
16756
33411
50067
66722
83378
100033
116689
133344
150000
Number of top SNPs(pruned)
score systems
CM3
LogOR


daner_scz_top8_eur
0.65
0.60
0.55
0.50
AUC
0
50000
100000
150000
Number of top SNPs(pruned)
score systems
CM3
LogOR

BIP


daner_bip2_top7_eur
Negelke R^2
0.025
0.020
0.015
0.010
0.005
0.000
100
16756
33411
50067
66722
83378
100033
116689
133344
150000
Number of top SNPs(pruned)
score systems
CM3
LogOR


daner_bip2_top7_eur
AUC
0.58
0.56
0.54
0
50000
100000
150000
Number of top SNPs(pruned)
score systems
CM3
LogOR

Acknowledgement

- NORMENT – TOP Oslo
  - Srdjan Djurovic, Verena Zuber, Yunpeng Wang, Francesco Bettella
- San Diego
  - Anders Dale, Wes Thompson, Andrew Schork, Anna Devor, Rahul Desikan, Linda McEvoy
- PGC – Psychiatric Genomics Consortium
- Collaborating consortia

References

1. Schork et al. All SNPs are not created equal: Genome-wide association studies reveal a consistent pattern of enrichment among functionally annotated SNPs. *PLoS Genetics* 2013 April 25
2. Andreassen et al. Improved detection of common variants associated with schizophrenia and bipolar disorder using pleiotropy-informed conditional False Discovery Rate. *PLoS Genetics* 2013 April 25
3. Andreassen et al. Improved Detection of Common Variants Associated with Schizophrenia by Leveraging Pleiotropy with Cardiovascular-Disease Risk Factors. *Am J Hum Genet*. 2013, 92, 1–13.
4. Liu et al. Dense genotyping of immune-related disease regions identifies nine new risk loci for primary sclerosing cholangitis. *Nat Genet* 2013 April 21
5. Andreassen et al. Genetic pleiotropy between multiple sclerosis and schizophrenia but not bipolar disorder: differential involvement of immune-related gene loci. *Mol Psychiatry*. 2014 Jan 28.
6. Andreassen et al. Identifying Common Genetic Variants in Blood Pressure Due to Polygenic Pleiotropy With Associated Phenotypes. *Hypertension*. 2014 Jan 6.
7. Andreassen OA, Thompson WK, Dale AM. Boosting the Power of Schizophrenia Genetics by Leveraging New Statistical Tools. *Schizophr Bull.* 2014 Jan;40(1):13-7.
8. Zablocki et al. Covariate-Modulated Local False Discovery Rate for Genome-wide Association Studies. *Bioinformatics*. In press.
9. Andreassen, Zuber et al. Shared common gene variants in prostate cancer and blood lipids. *Int J Epidemiol.* In press.