Extended

Mode

Autism dat

Schizophren

data

Data

Results:includeEXAC

Risk genes Itersect with

gene sets

Intersect wit

May, 2015

May 2, 2016

Schizophre

Data
Methods
Results:includeEXAC
Risk genes
Itersect with

gene sets Results:NotEXAC Risk genes Intersect with Review exTADA (Transmission And De novo Association) model.

- Test exTADA on autism data.
- Apply exTADA to schizophrenia data.
 - Estimate the proportion of risk genes.
 - Test results on gene sets.

Extendo TADA Model

Autism data

Schizophre

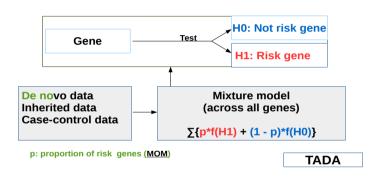
Data

Results:includeEXAC

Itersect with gene sets

Results:NotEX/

Risk genes Intersect with gene sets



PLoS Genet. 2013;9(8):e1003671. doi: 10.1371/journal.pgen.1003671. Epub 2013 Aug 15.

Integrated model of de novo and inherited genetic variants yields greater power to identify risk genes.

He X1, Sanders SJ, Liu L, De Rubeis S, Lim ET, Sutcliffe JS, Schellenberg GD, Gibbs RA, Daly MJ, Buxbaum JD, State MW, Devlin B, Roeder K.

Original TADA

- Use only LoF de novo mutations => the proportion of risk genes (π) **
- Use known risk genes AND ** to infer other information of other categories.

Extended TADA

- Estimate simultaneously all parameters of all annotations (e.g., LoF, missense damaging) including π
- Do not use known risk genes (it can be used, but not neccessary).

ExTADA

Review TADA

Extend TADA Model

Autism data

Schizophrer

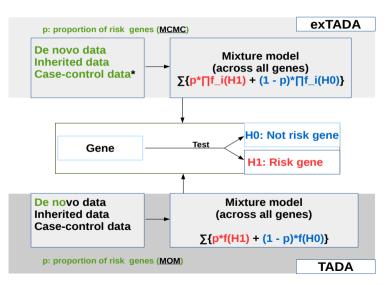
Methods

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Intersect with



Schizophrenia
data
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gene sets
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Main work

- De novo mutations: the same as original TADA.
- Inherited/Case-control: use an approximate model as original TADA in the estimation process ¹.
- Estimate all parameters using a MCMC method (known risk genes are not neccessary).

Model: Internal product

```
P(x|\textit{paramterers}) = \prod_{i=1}^{m} \left[ \pi P(x_{i_{LOF}}|H_1) P(x_{i_{mis3}}|H_1) + (1-\pi) P(x_{i_{LOF}}|H_0) P(x_{i_{mis3}}|H_0) \right]
```



¹Idea of changing case-control model is from Xin He

Schizophrei

Data Methods

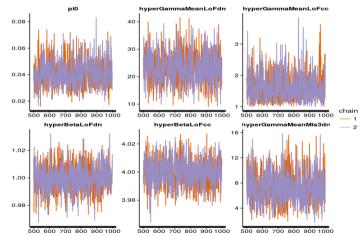
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Risk genes
Intersect wit
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Autism Data

Use **noninformation priors** => similar results as TADA (based on known risk genes)



Schizophrenia data

Review TADA

Extended TADA Model

Autism data

Data
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Results:includeEXAC
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Results:NotEXA Risk genes Intersect with gene sets Sample sizes from different studies.

Source	De novo	Non/Transmitted	Case	Control
Fromer et al. (2014)	617	617		
Girard et al. (2011)	14			
Gulsuner et al. (2013)	105			
McCarthy et al. (2014)	57			
Xu et al. (2012)	231			
Giulio et al. (2016)			4954	6239
Total	1024	617	4954	6239

Schizophrenia
data
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Risk genes
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gene sets

Focused on:

• De novo (DN) + Transmitted (Trans) + Case-Control (CC).

Also tested:

- De novo (DN) + Transmitted (Trans).
- De novo (DN) + Case-Control (CC).
- De novo (DN).

Categorieis: LoF and missense damaging (7 methods from Giulio). Private (Not in Exac) or Non-private (include Exac).

Schizophre

Data
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Results:includeEXAC
Risk genes
Itersect with
gene sets
Results:NotEXAC
Risk genes

Previous studies (The unseen species problem):

- Xu et al (2012): **868 genes** based on 231 parent-proband trios and 34 unaffected trios.
- Fromer et al (2014): 4000 to 12000 genes based on 623 schizophrenia trios (use LoF and NS mutations).

How many risk genes from exTADA?

Singleton data + NOT private.

Review TADA

Extende TADA Model

Autism dat

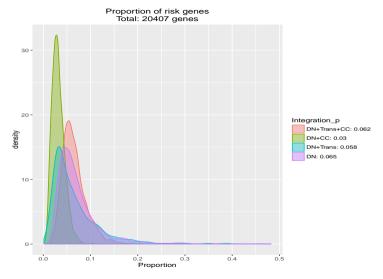
Schizophrer

Data

Results:includeEXAC
Risk genes

Itersect with gene sets

gene sets Results:NotEXA Risk genes



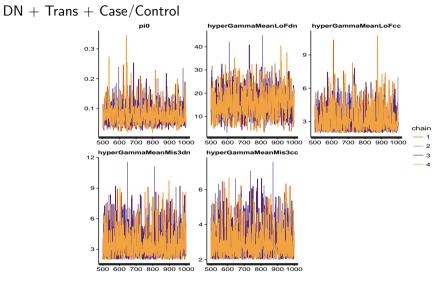
data

Data Methods

Results:includeEXAC
Risk genes
Itersect with

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Risk genes
Intersect with
gene sets



Schizophrer

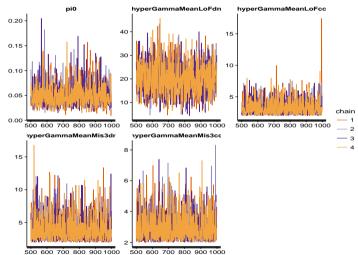
data Data

Results:includeEXAC Risk genes

gene sets
Results:NotEXA

Risk genes
Intersect with

$\mathsf{DN} + \mathsf{Case}/\mathsf{Control}$



Schizophreni data

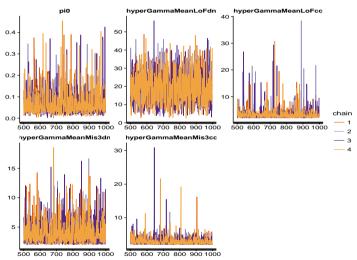
Methods Results:includeEXAC

Risk genes

gene sets

Risk genes
Intersect with

DN + Trans



view TADA DN

Extende TADA

Autism dat

Schizophre

Data

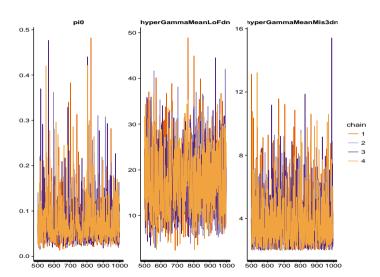
Results:includeEXAC

Risk genes

gene sets

Results:NotEX

Intersect wi



Schizophrenia
data
Data
Methods
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Itersect with
gene sets
Results:NotEXAC

Choose top genes (e.g., FDR < 0.3 or top 100 genes) from exTADA results (n = IGene) + download know gene sets.

Calculate p value for each gene set (N genes)

- Count the number of genes overlapping between the *IGene* genes and the gene set, nG.
- For i from 1 to K (times)
 - Randomly choose a set of N genes from all genes (>20000 genes).
 - Count the number of genes overlapping between the *IGene* genes and the random gene set, M_i .
 - pValue = (length(vM[vM >= nG]) + 1)/(K + 1)with $vM = c(M_1, M_2, ...M_K)$

Extended

Mode

Autism data

California de la constitución

SCIIIZO

data

Data

Results:includeEXAC

Risk genes

Itersect with gene sets

Risk genes

Extende TADA Model

Autism data

Schizophren

Data

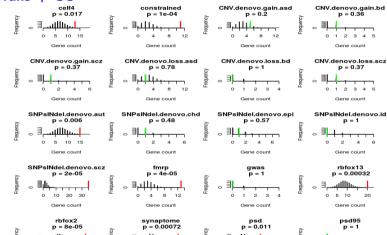
Methods
Results:includeEXAC

Risk genes Itersect with gene sets

Results:NotEXA Risk genes

Intersect with gene sets

DN + Trans + CC



10 15

Gene count

Gene count

Gene count

3

Gene count

Extended TADA Model

Autism data

Schizophren

Data

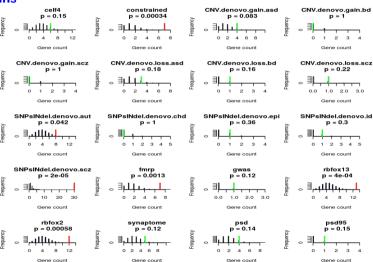
Methods
Results:includeFXAC

Risk genes Itersect with

gene sets
Results:NotEXA(

Intersect with gene sets

DN + Trans



Pavious TADA

Extended

Mode

Autism data

C-12----

Schizophre

data

Data

Results:includeEXAC

Risk genes

Itersect with gene sets

Results:NotEXAC

Intersect with gene sets

Paviou TADA

Extended TADA Model

Autism data

Schizophren

Data

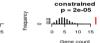
Methods
Results:includeEXAC

Risk genes Itersect with

gene sets
Results:NotEXA

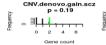
Intersect with gene sets

DN + Trans + CC







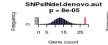


Gene count





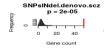


























Schizophrer

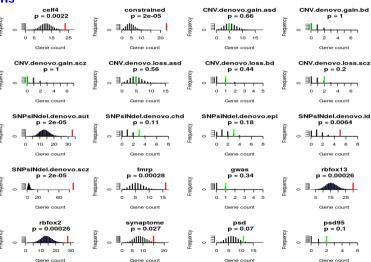
Data Methods

Results:includeEXAC

Risk genes Itersect with gene sets

Risk genes
Intersect with

DN + Trans

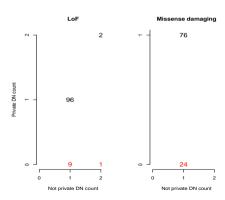


Results:includeFXAC

Results: NotEXAC

 Remove all variants in EXAC (= Private variants) => lose 1 LoF double-hit gene.

Use the same mutation rates. ²



²Re-calculating mutation rates by removing all Exac variants ←□ → ←② → ←② → ←② → ◆② → ◆② ←



Not EXAC

Review TADA

Extende TADA

Autism data

Schizophren

data

Methods

Results:includeEXAC

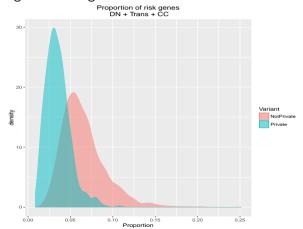
Risk genes

gene sets

Risk genes

Intersect with

Proportion of risk genes not high



Not EXAC

Review TADA

Extended

Autism dat

Schizophreni data

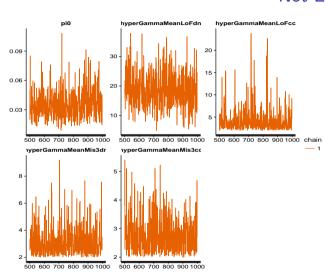
Data

Results:includeEXAC

Itersect with gene sets

Results:NotEXA

Intersect wit



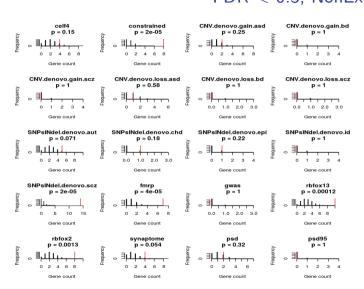
Schizophren

Data

Results:includeEXAC Risk genes Itersect with

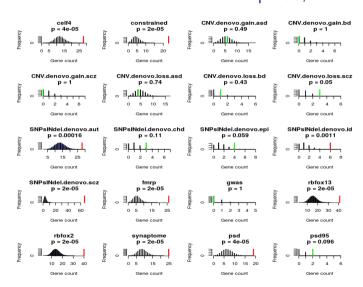
gene sets
Results:NotEXA

Intersect with



Results:includeFXAC

Intersect with gene sets



Results:includeEXAC

Intersect with gene sets

Private and Not private

Overlapping genes with different thresholds:

Include Exac FDR < 0.3 FDR < 0.1 Include Exac Not Exac Not Exac Include ExacNot Exa Top 100

data

Methods Results:includeEXAC Risk genes

Itersect with gene sets
Results:NotEXA

Intersect with gene sets

Overlapping genes: FDR < 0.1

Both LoF de novos of TAF13 are in Exac variants.

-			
Gene	NotPrivate	Private	
ADCY6	1	0	
BLNK	1	0	
EPHA5	1	0	
HEATR2	1	0	
MARK4	1	0	
MPO	1	0	
PRRC2A	1	0	
ROBO1	1	0	
TAF13	1	0	
RB1CC1	1	1	
SETD1A	1	1	

Extended

Mode

Autism data

Cabinanhuani

data

Data

Results:includeEXAC

Risk genes

gene sets

Risk genes
Intersect with

resect with

THANK YOU!!!!!