

May, 2015

Review TADA

Extended
TADA
Model

Autism data

Schizophrenia
data

Data
Methods
Results:includeEXAC

Risk genes
Intersect with
gene sets
Results:NotEXAC

Risk genes
Intersect with
gene sets

May, 2015

May 2, 2016

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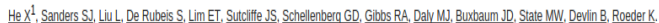
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- Review exTADA (Transmission And De novo Association) model.
- Test exTADA on autism data.
- Apply exTADA to schizophrenia data.
 - Estimate the proportion of risk genes.
 - Test results on gene sets.

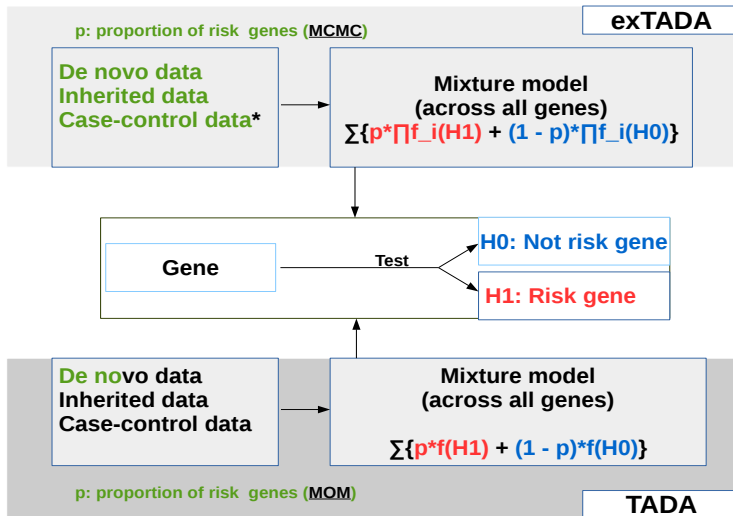


Original TADA

- Use only LoF de novo mutations \Rightarrow 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 necessary).



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 necessary).

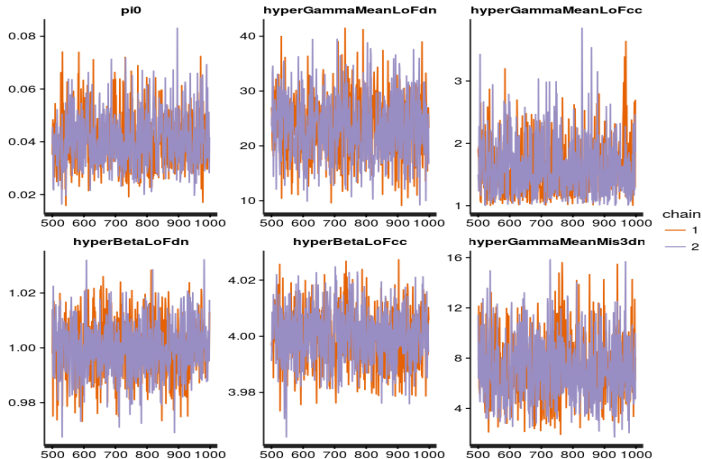
Model: **Internal product**

$$P(x|parameters) = \prod_{i=1}^m \left[\pi P(x_{i_{LoF}} | H_1) P(x_{i_{mis3}} | H_1) + (1 - \pi) P(x_{i_{LoF}} | H_0) P(x_{i_{mis3}} | H_0) \right]$$

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

Autism Data

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



Schizophrenia data

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

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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).

How many risk genes

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Risk genes

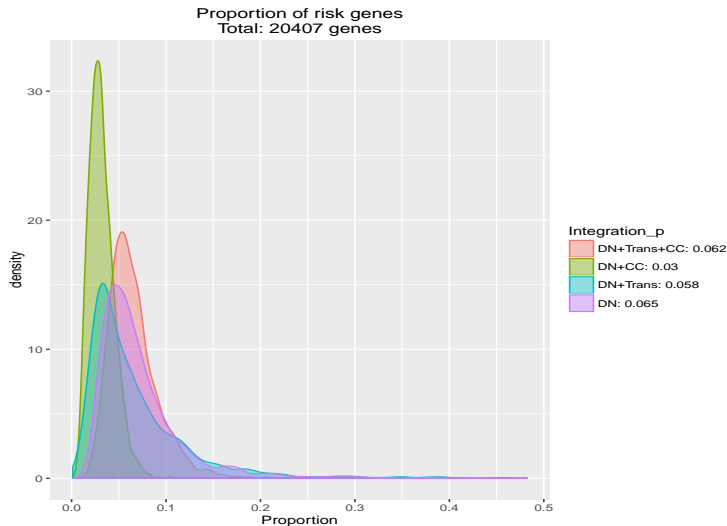
Intersect with
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Previous studies (The unseen species problem):

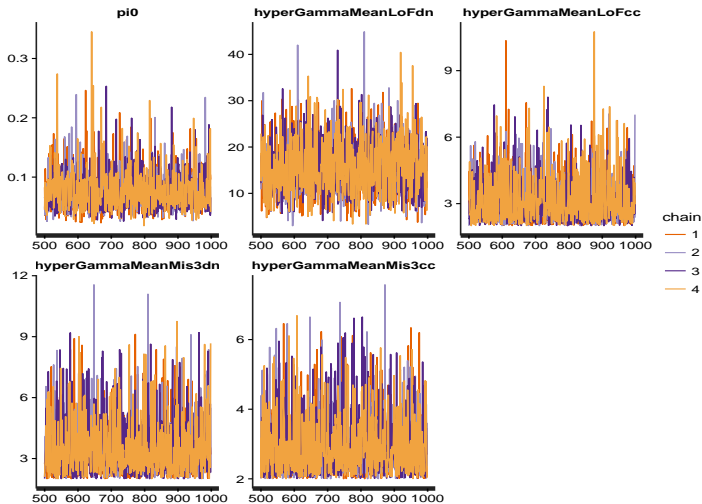
- Xu et al (2012): **868 genes** based on 231 parent-proband trios and 34 unaffected trios.
- Fromer et al (2014): **4000 to 12000 genes** based on 623 schizophrenia trios (use LoF and NS mutations).

How many risk genes from exTADA?

Singleton data + NOT private.



DN + Trans + Case/Control



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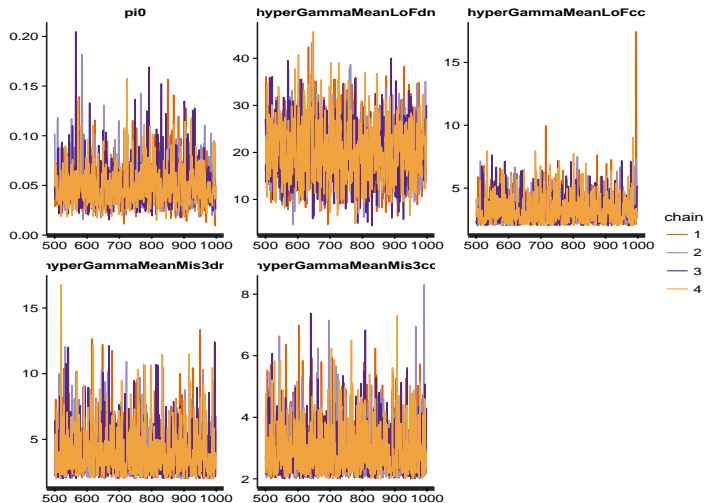
Results:NotEXAC

Risk genes

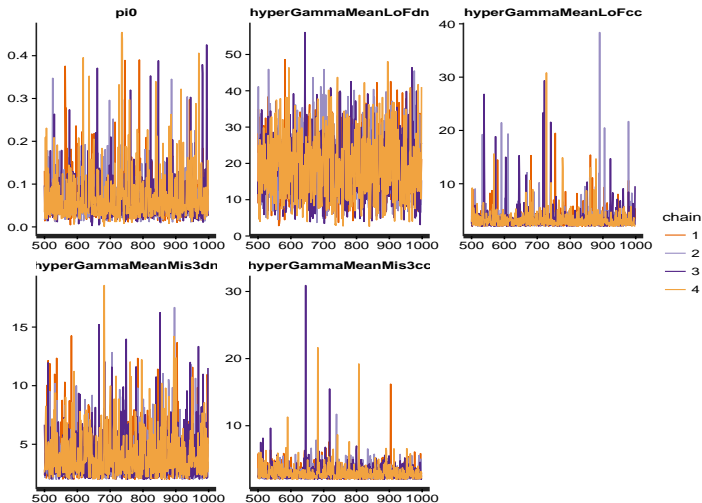
Intersect with

gene sets

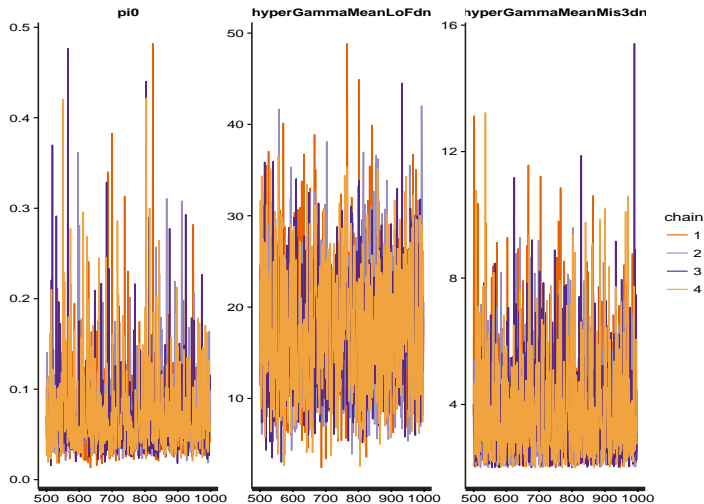
DN + Case/Control



DN + Trans



DN



Intersect with known gene sets

Choose top genes (e.g., $FDR < 0.3$ or top 100 genes) from exTADA results ($n = I_{Gene}$) + download known gene sets.

Calculate p value for each gene set (N genes)

- Count the number of genes overlapping between the I_{Gene} genes and the gene set, n_G .
- 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 I_{Gene} genes and the random gene set, M_i .
 - $pValue = (length(vM[vM \geq n_G]) + 1) / (K + 1)$
with $vM = c(M_1, M_2, \dots, M_K)$

FDR < 0.3

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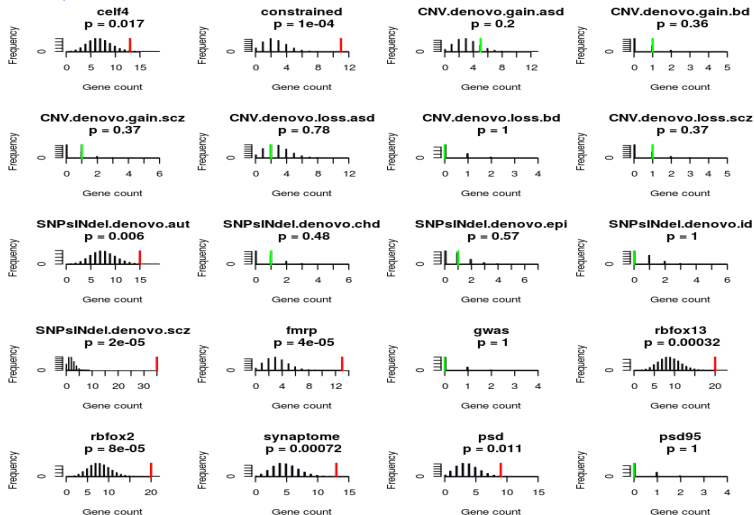
Results:NotEXAC

Risk genes

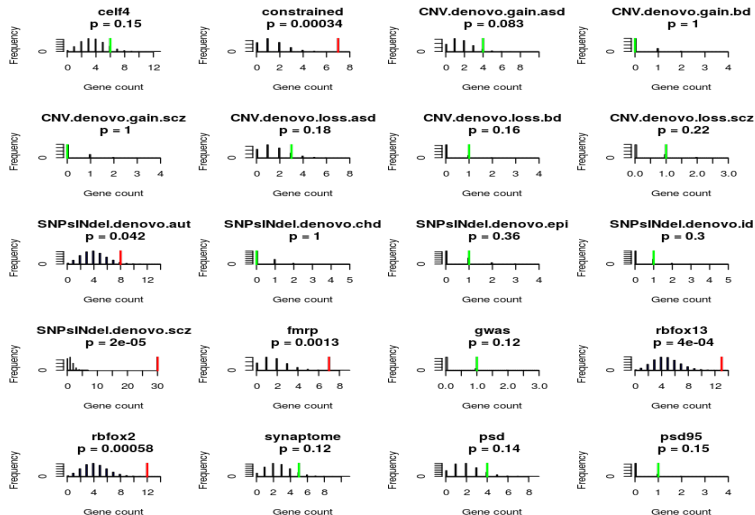
Intersect with
gene sets

FDR < 0.3

DN + Trans + CC



DN + Trans



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Top 100 genes

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**Intersect with
gene sets**

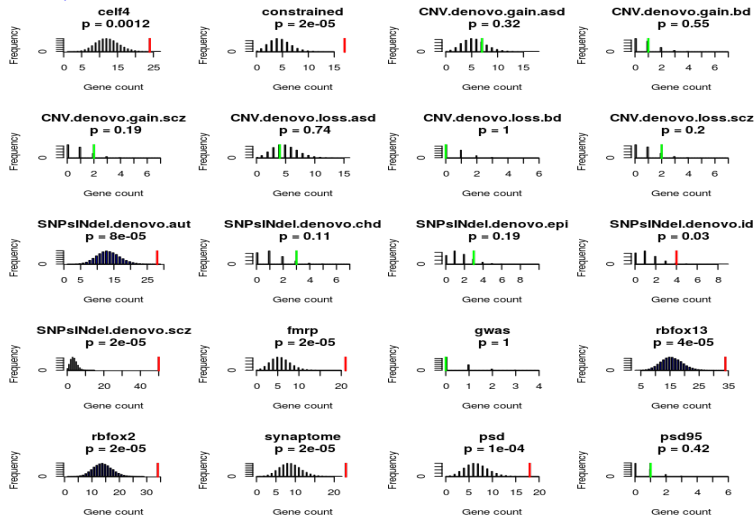
Results:NotEXAC

Risk genes

Intersect with
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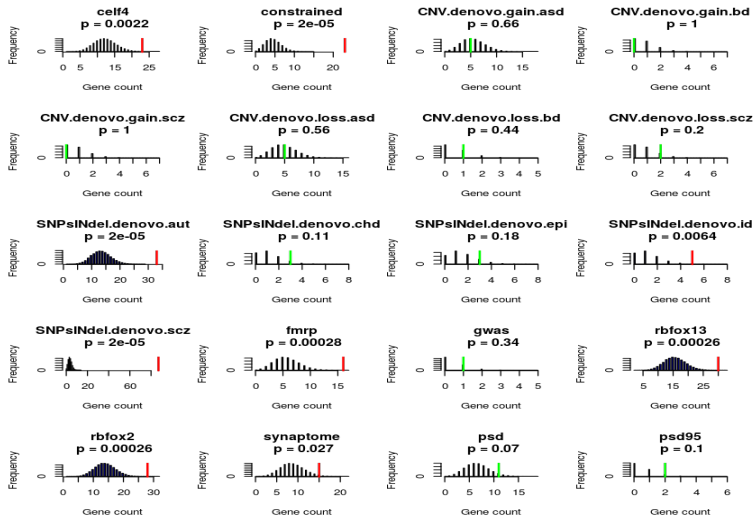
Top 100 genes

DN + Trans + CC



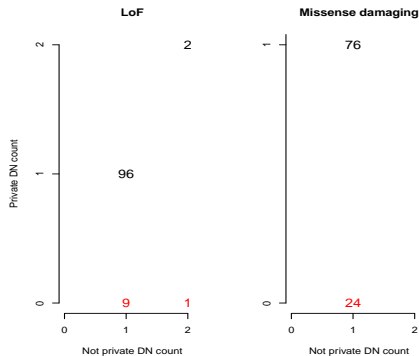
Top 100 Genes

DN + Trans



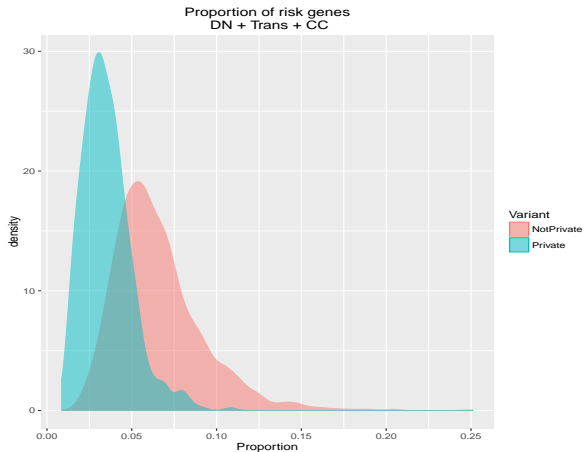
Not EXAC

- 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

Proportion of risk genes not high



Not EXAC

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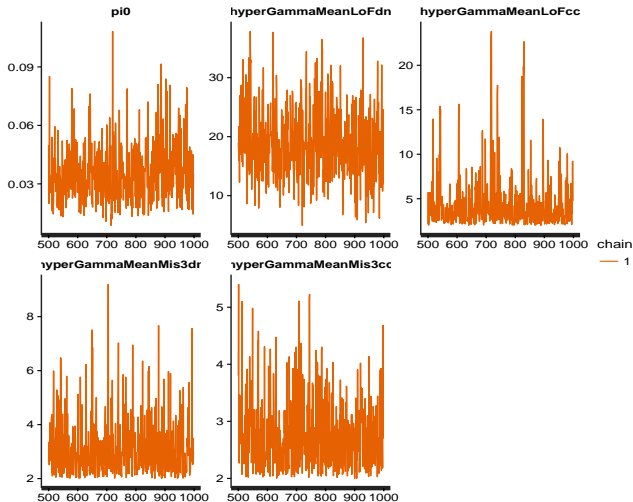
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FDR < 0.3, NonExac

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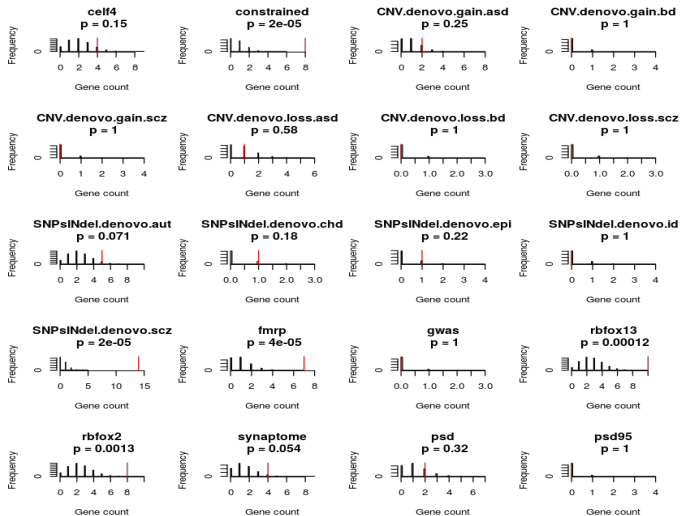
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Top 100, NonExac

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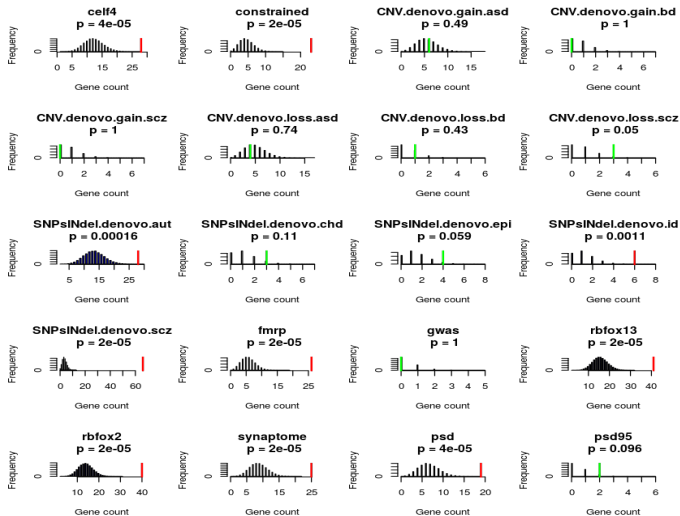
Results:includeEXAC

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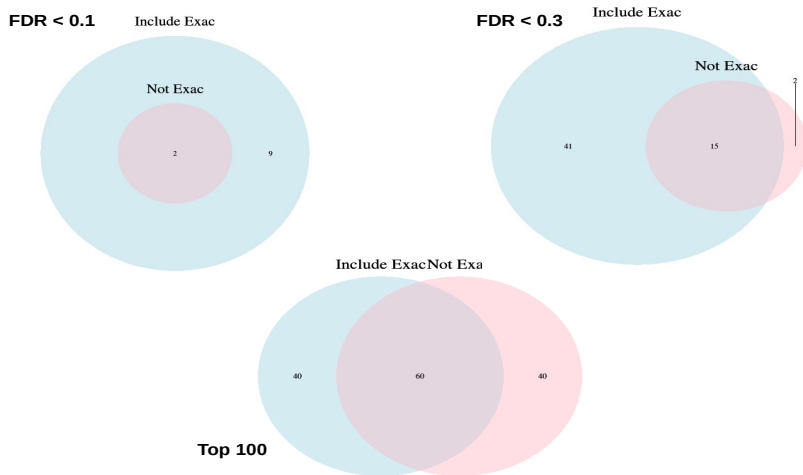
Results:NotEXAC

Risk genes

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Private and Not private

Overlapping genes with different thresholds:



Overlapping genes

Overlapping genes: $\text{FDR} < 0.1$

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

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Risk genes

**Intersect with
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THANK YOU!!!!!!