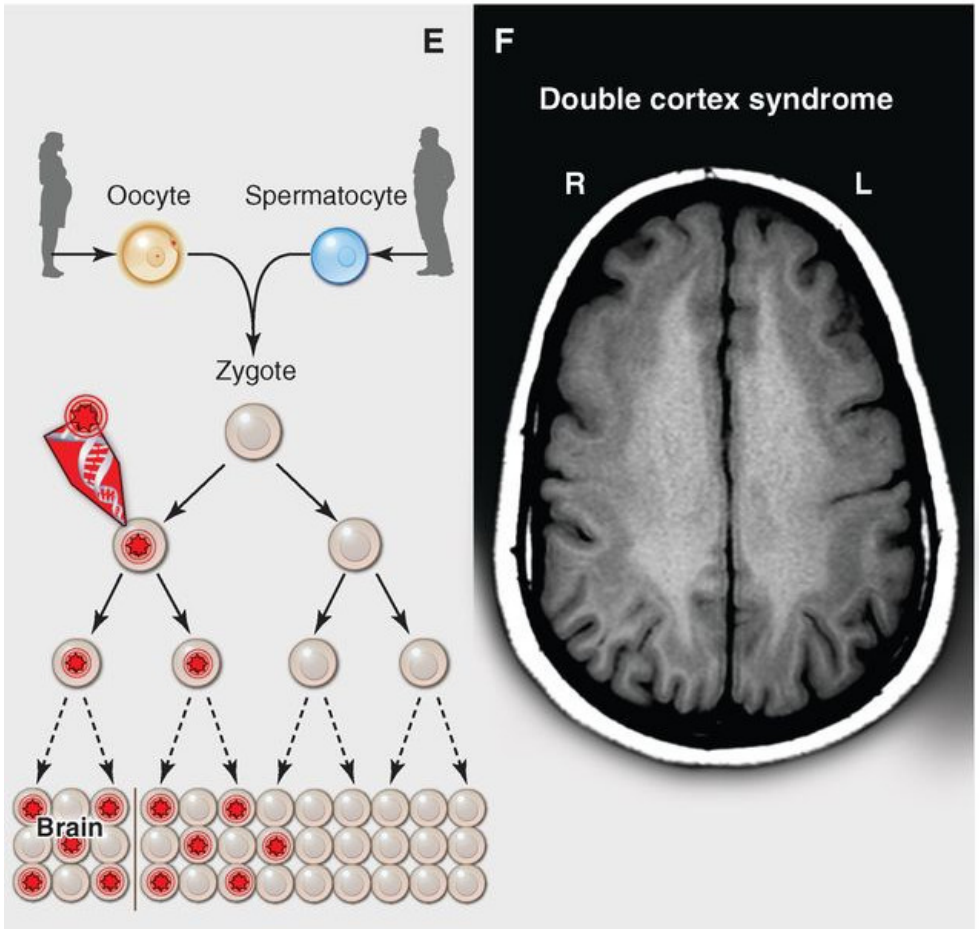
Brain somatic mosaicism in schizophrenia



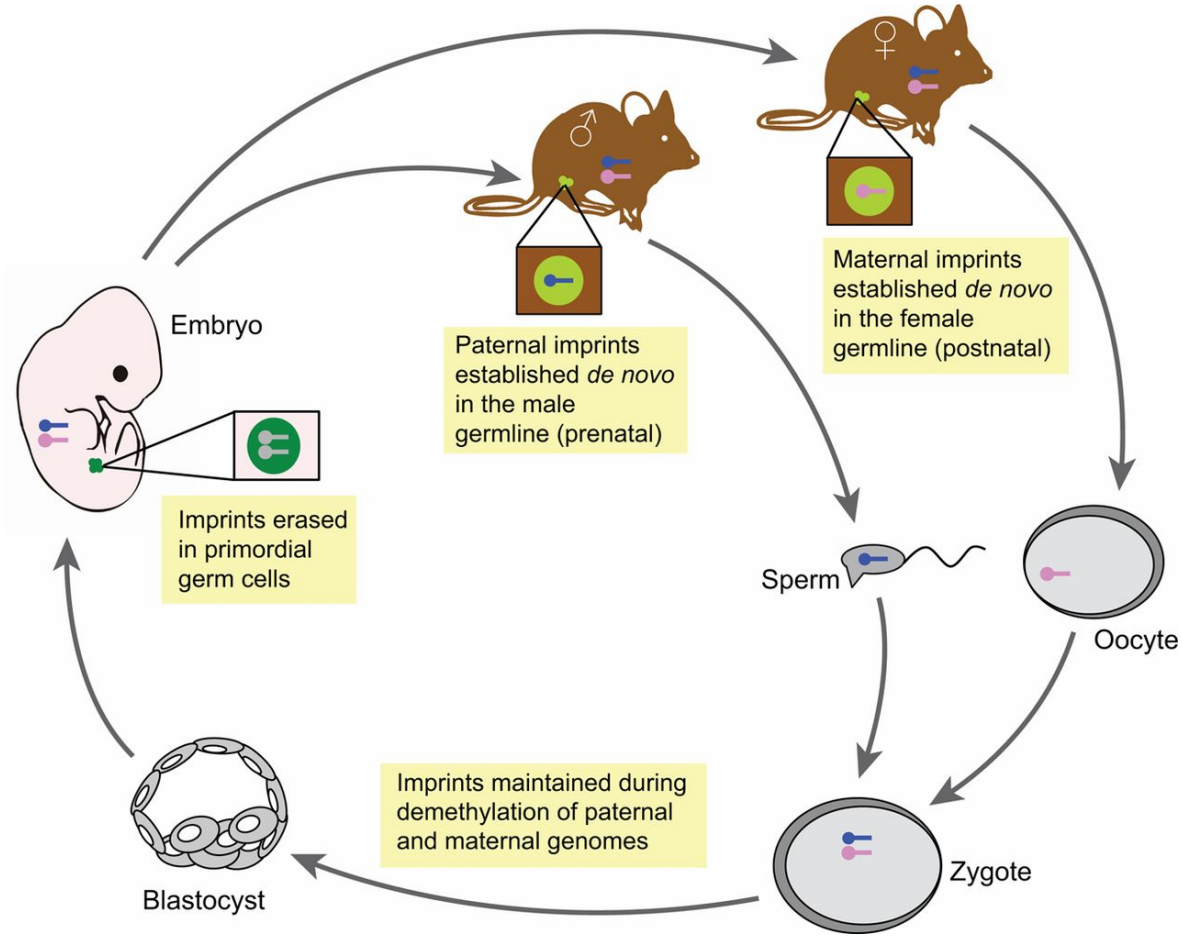
Genomic Imprinting in the Human Brain

Links to Aging, Gender, and Schizophrenia

Attila Gulyás-Kovács

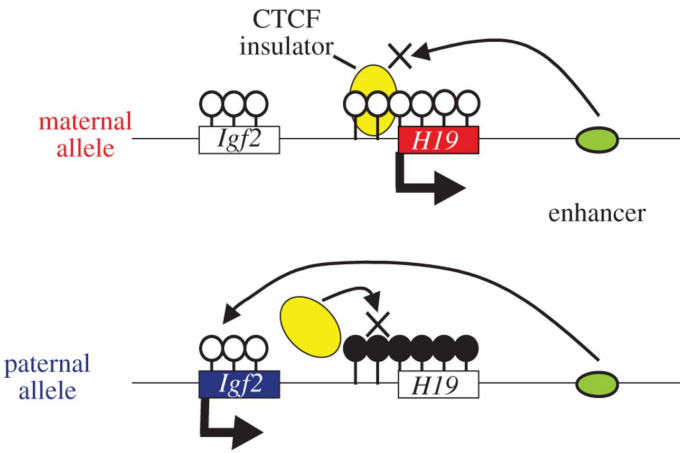
Chess Lab

Genomic imprints during development

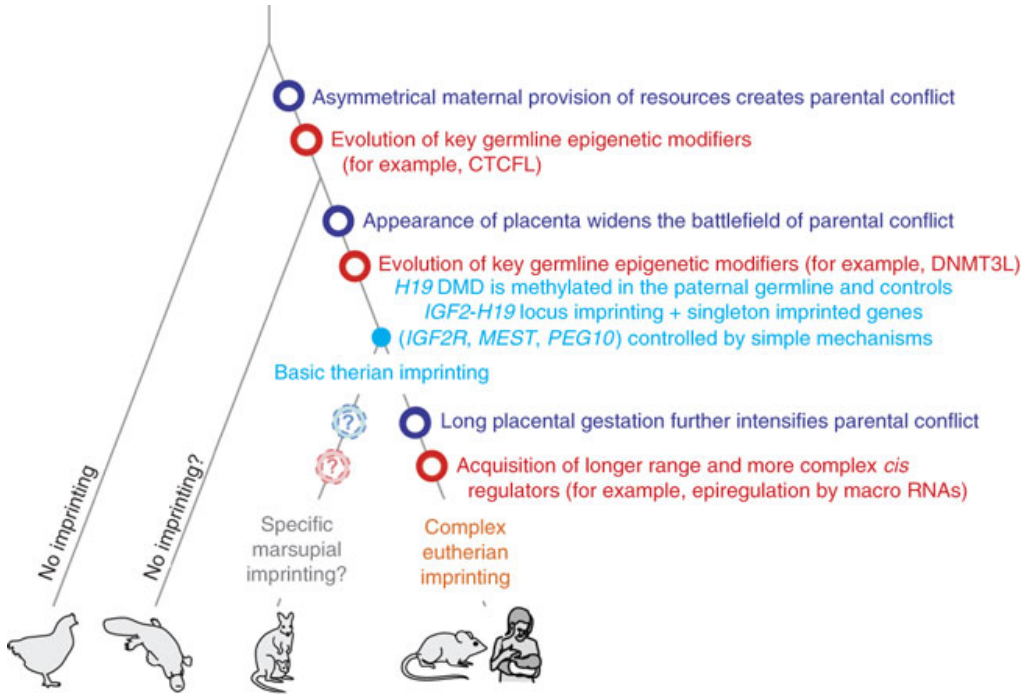


Plasschaert & Bartolomei 2014 Development.

Parental bias and placental development

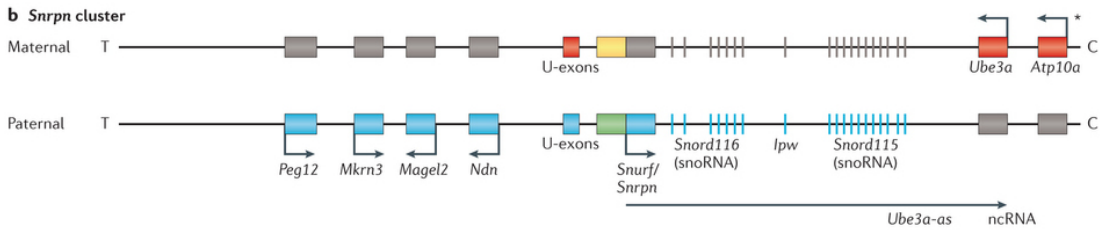


Renfree et al 2012 Philos Trans R Soc Lond B



Smits et al 2008 Nat Genet

Sister disorders, neuropsychiatric functions



Peters 2014 Nat Rev Genet.

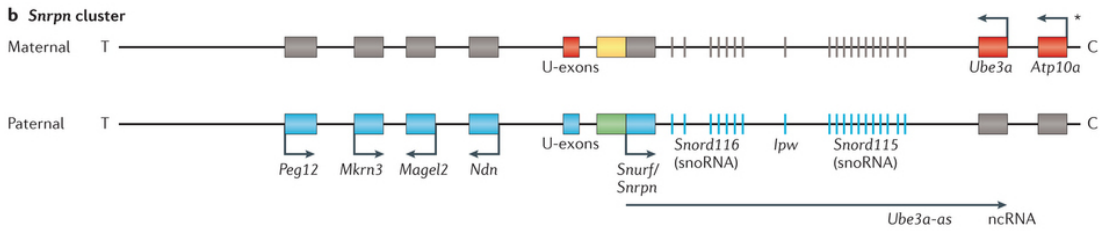
Angelman syndrome

Boy with a Puppet

Prader-Willi syndrome

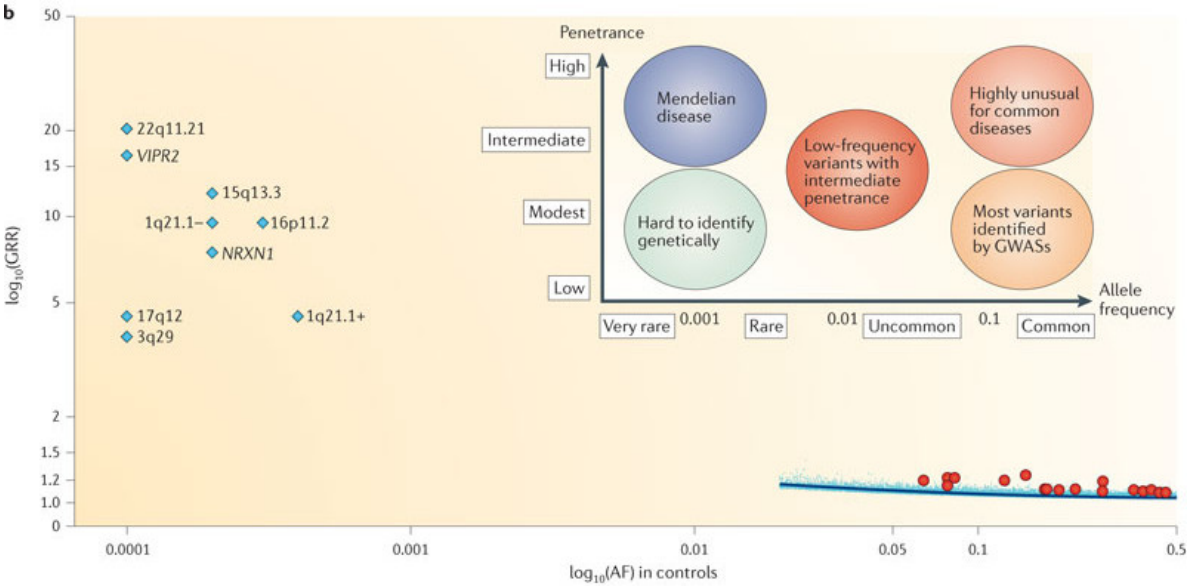
Eugenia Martínez Vallejo

Sister disorders, neuropsychiatric functions



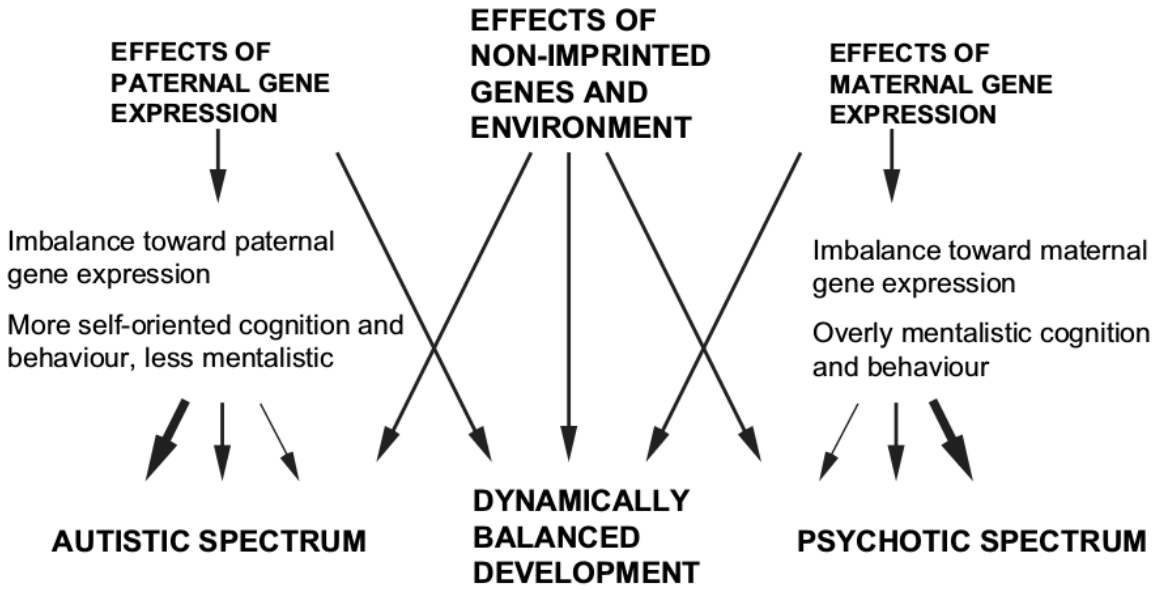
Peters 2014 Nat Rev Genet.

genetic architecture of schizophrenia



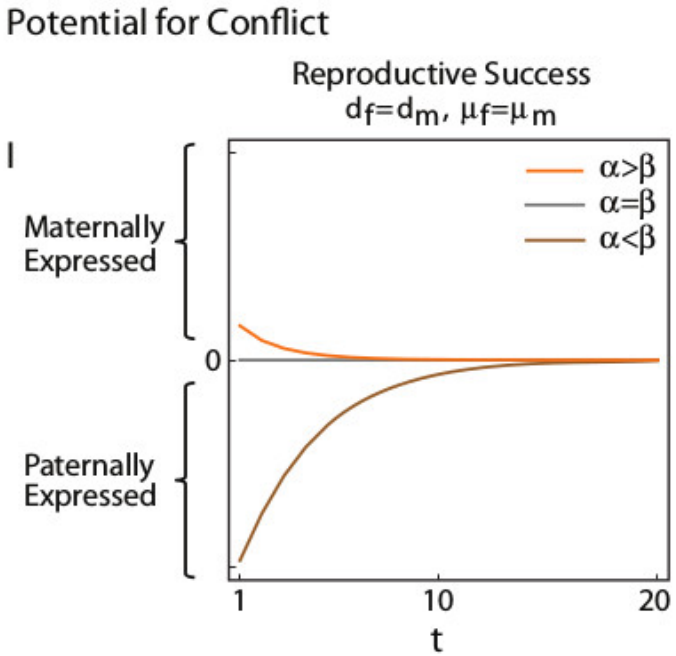
Nature Reviews | Genetics Sullivan 2012 Nat Rev Genet.

The imprinted brain theory

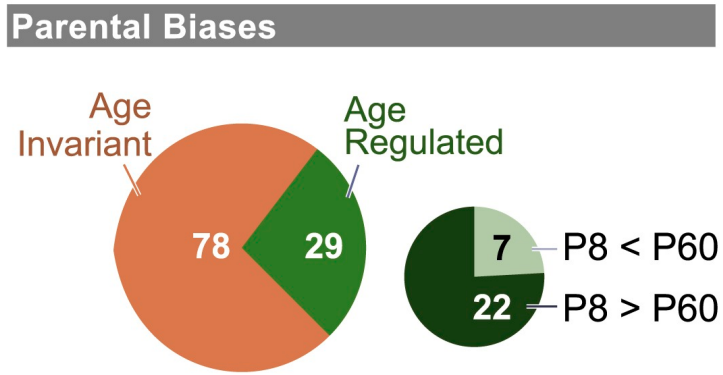


Crespi & Badcock 2008 Behav Brain Sci.

Explaining variation of parental bias: age



Ubeda 2012 Evolution



Perez et al 2015 eLife

Our research study

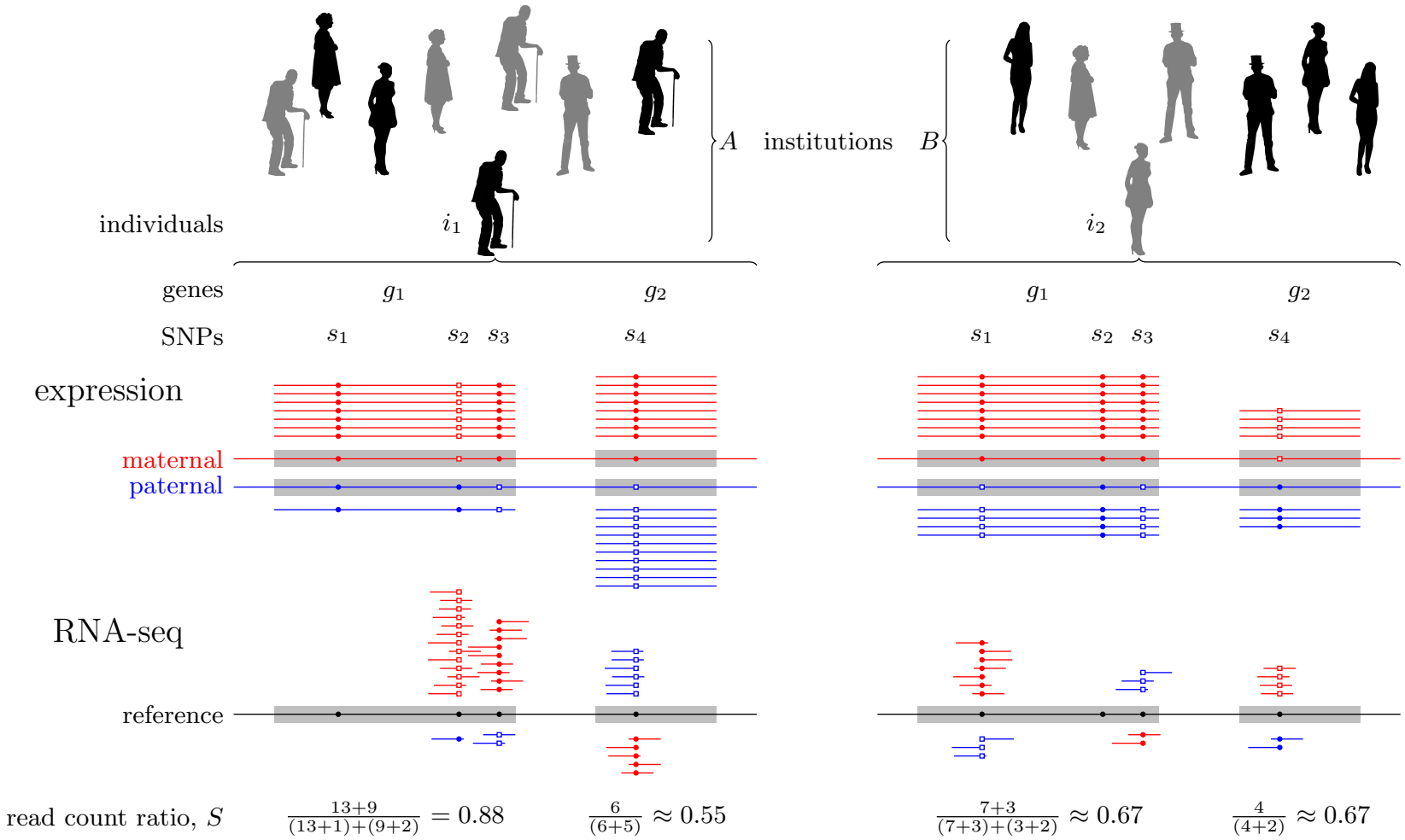
data/project Common Mind Consortium

questions imprinted genes in the human brain

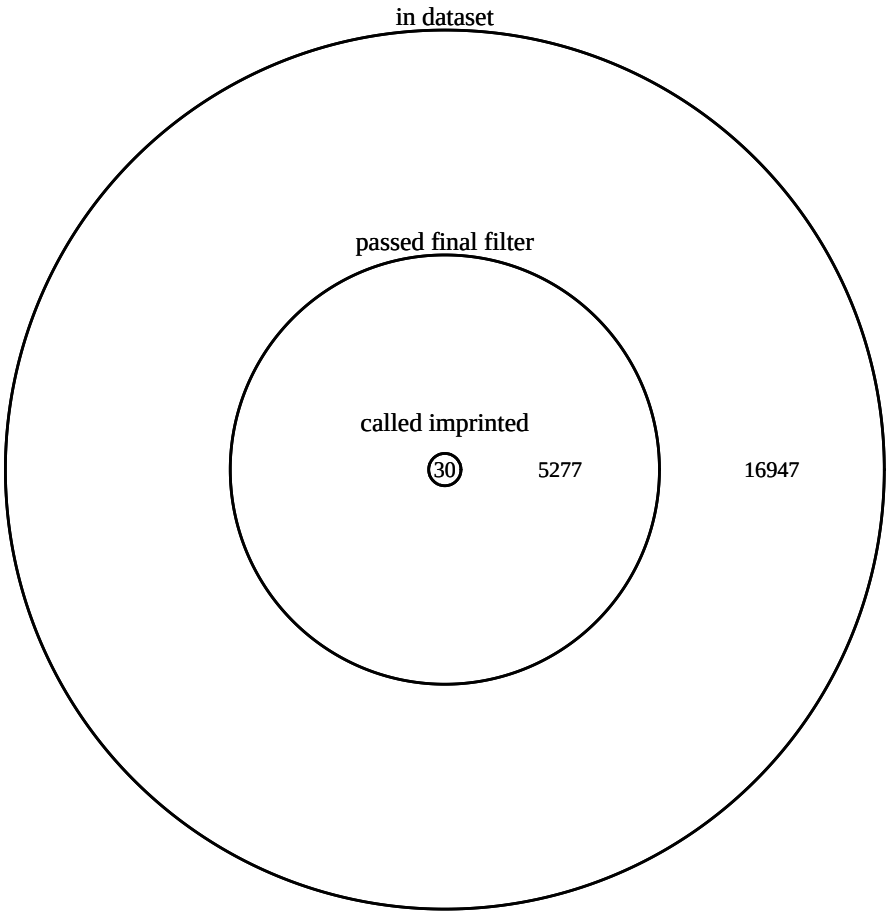
- variation of parental bias across genes and individuals
- regulators: age, gender, genotype (ancestry)
- psychiatric disorders (SCZ, AFF)

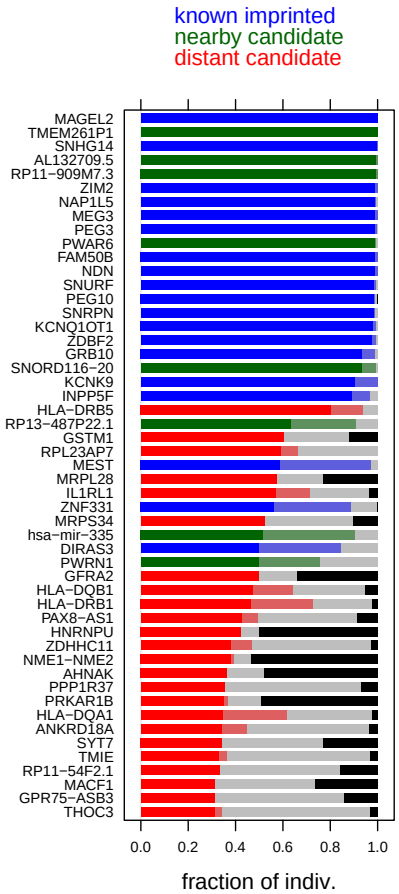
participants Ifat Keydar, Eva Xia, Menachem Fromer, Doug Ruderfer, Ravi Sachinanandam, Andrew Chess

The Common Mind data

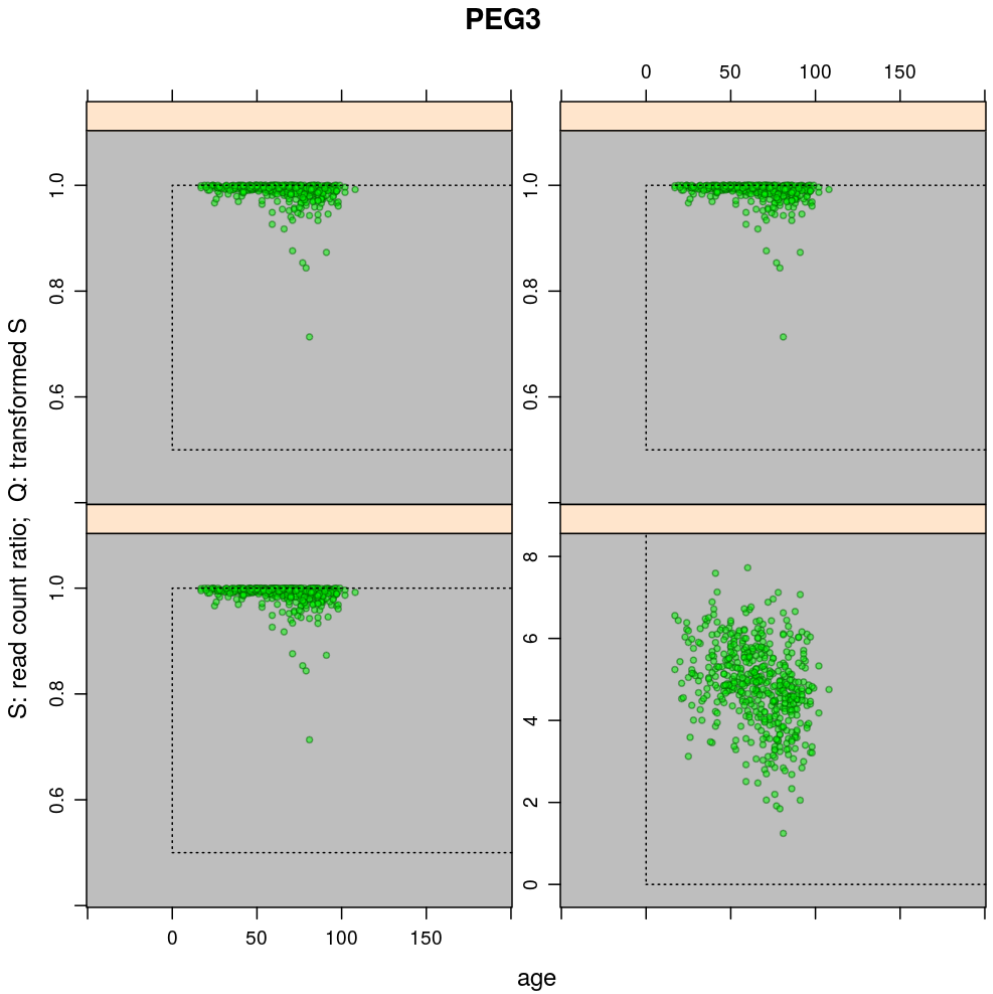


Calling imprinted genes



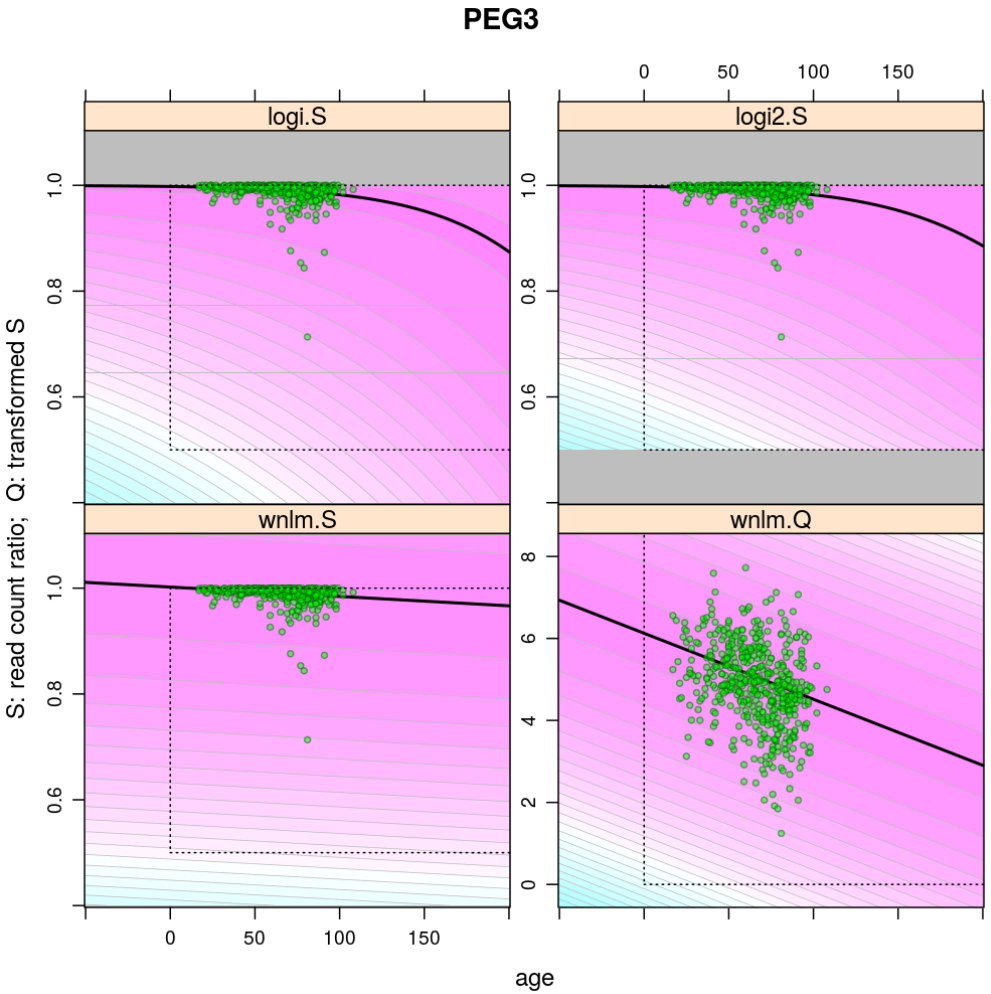


Explaining variation of parental bias with predictors



- Y_g from read count ratio
- X based on predictor(s)
- $\mathcal{H}_0$: no dependence

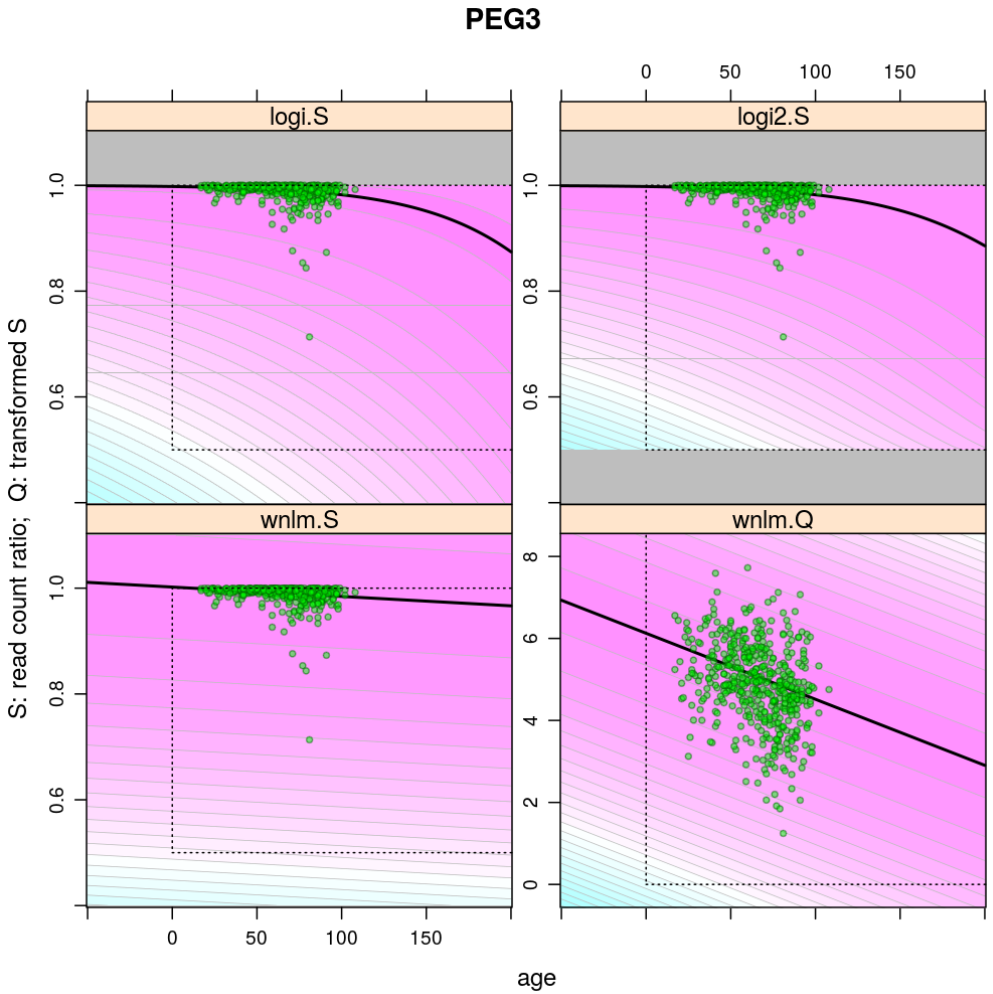
Explaining variation of parental bias with predictors



- Y_g from read count ratio
- X based on predictor(s)
- $\mathcal{H}_0$: no dependence $\Leftrightarrow \beta_g = 0$

$$Y_g = X\beta_g + \epsilon_g$$

Explaining variation of parental bias with predictors

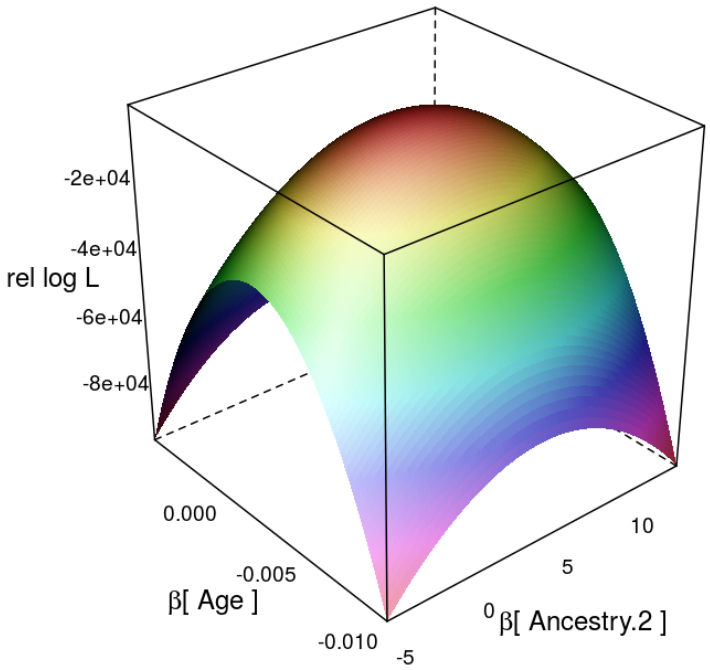


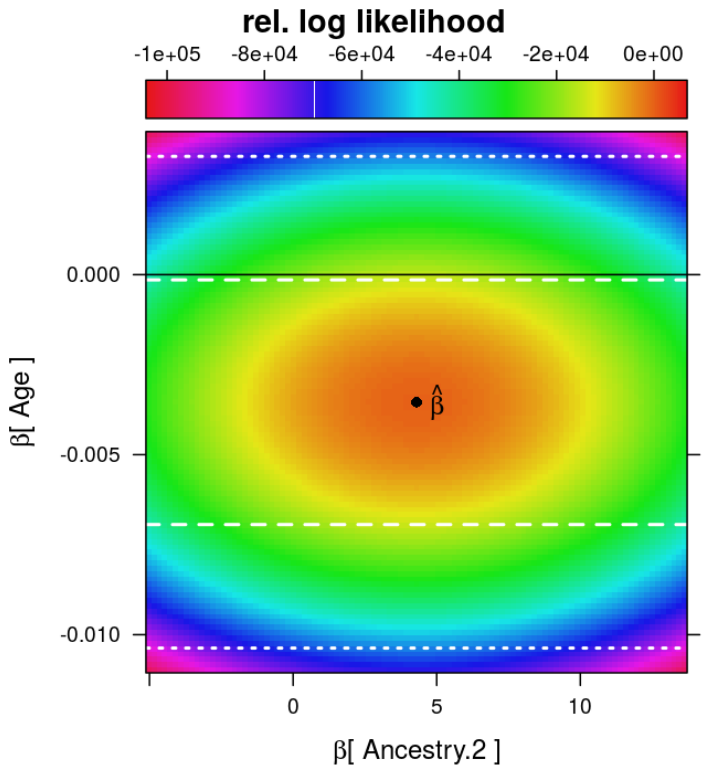
- Y_g from read count ratio
- X based on predictor(s)
- $\mathcal{H}_0$: no dependence $\Leftrightarrow \beta_g = 0$

$$Y_g = X\beta_g + \epsilon_g$$

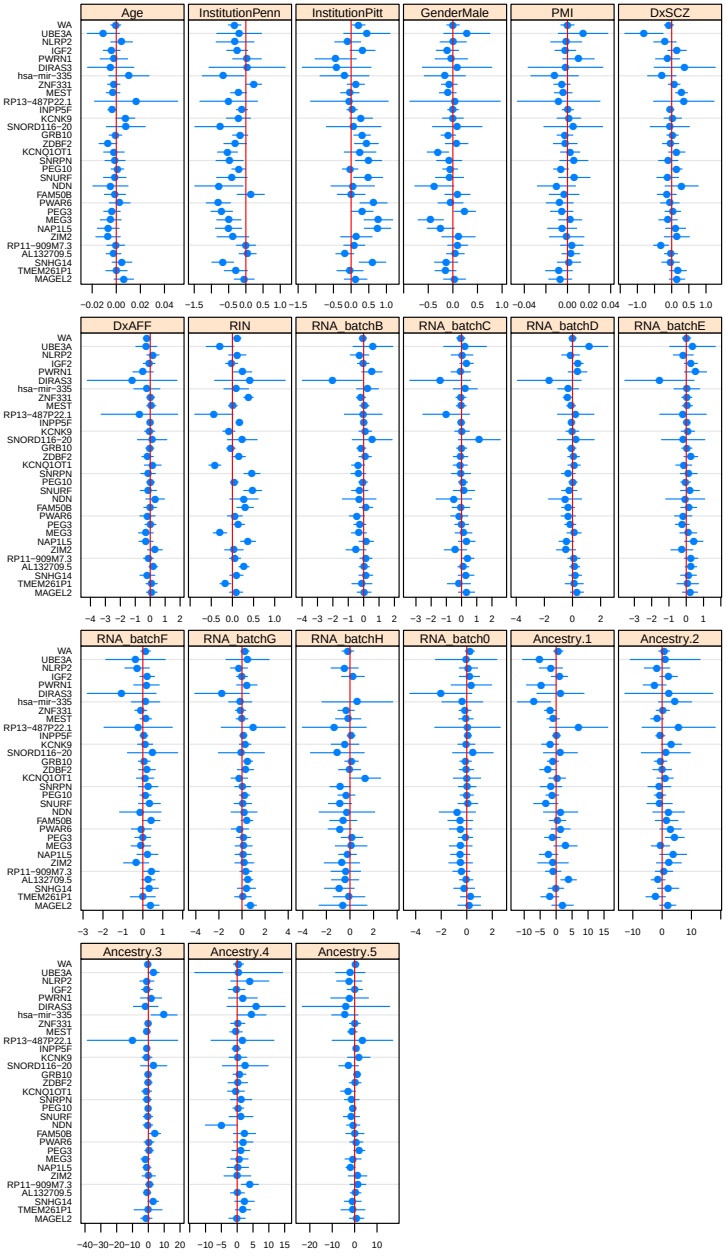
predictor	levels
Age	
Gender	Female, Male
Dx	AFF, Control, SCZ
Ancestry.1-5	
Institution	MSSM, Penn, Pitt
PMI	
RIN	
RNA_batch	0, A, B, C, D, E, F, G, H

Estimating β and testing for $\mathcal{H}_0 : \beta = 0$

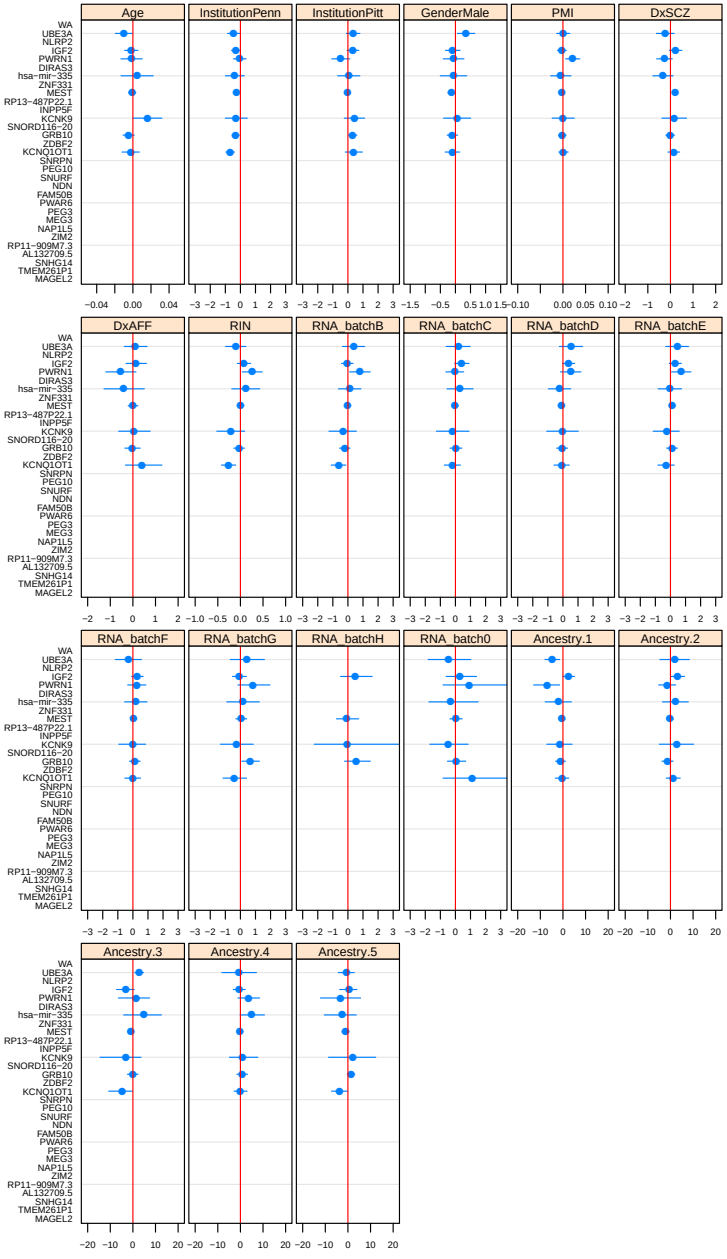




99 % CI for β under wnlm.Q

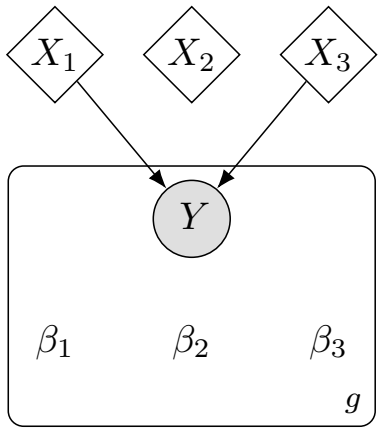


99 % CI for β under logi.S



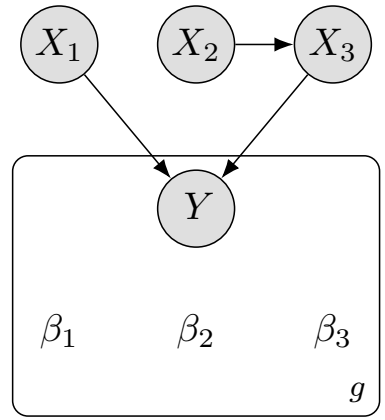
designed experiment

y	$x_{\cdot 1}$	$x_{\cdot 2}$	$x_{\cdot 3}$
y_1	-1	-1	-1
y_2	-1	-1	1
y_3	-1	1	-1
y_4	-1	1	1
y_5	1	-1	-1
y_6	1	-1	1
y_7	1	1	-1
y_8	1	1	1

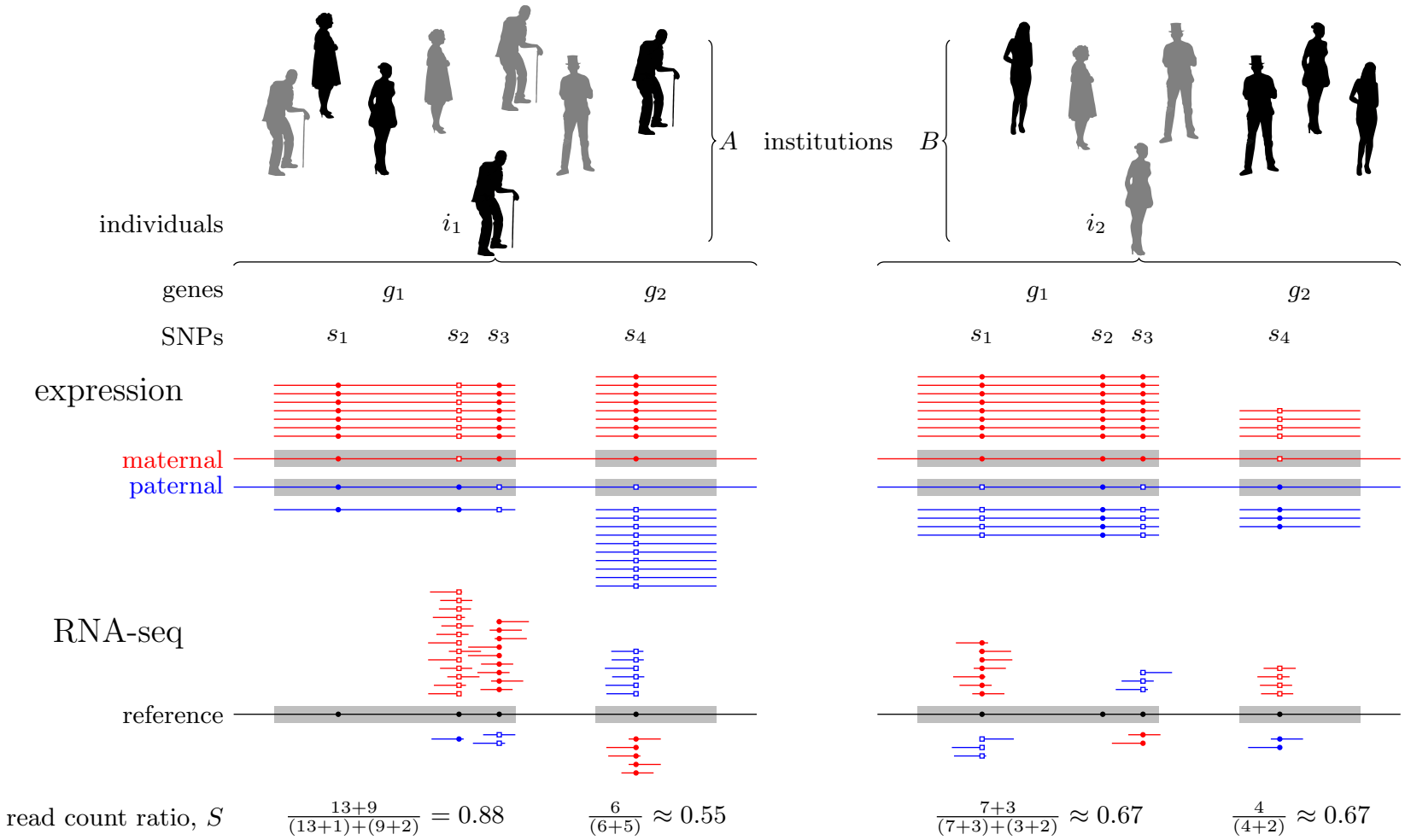


observational study

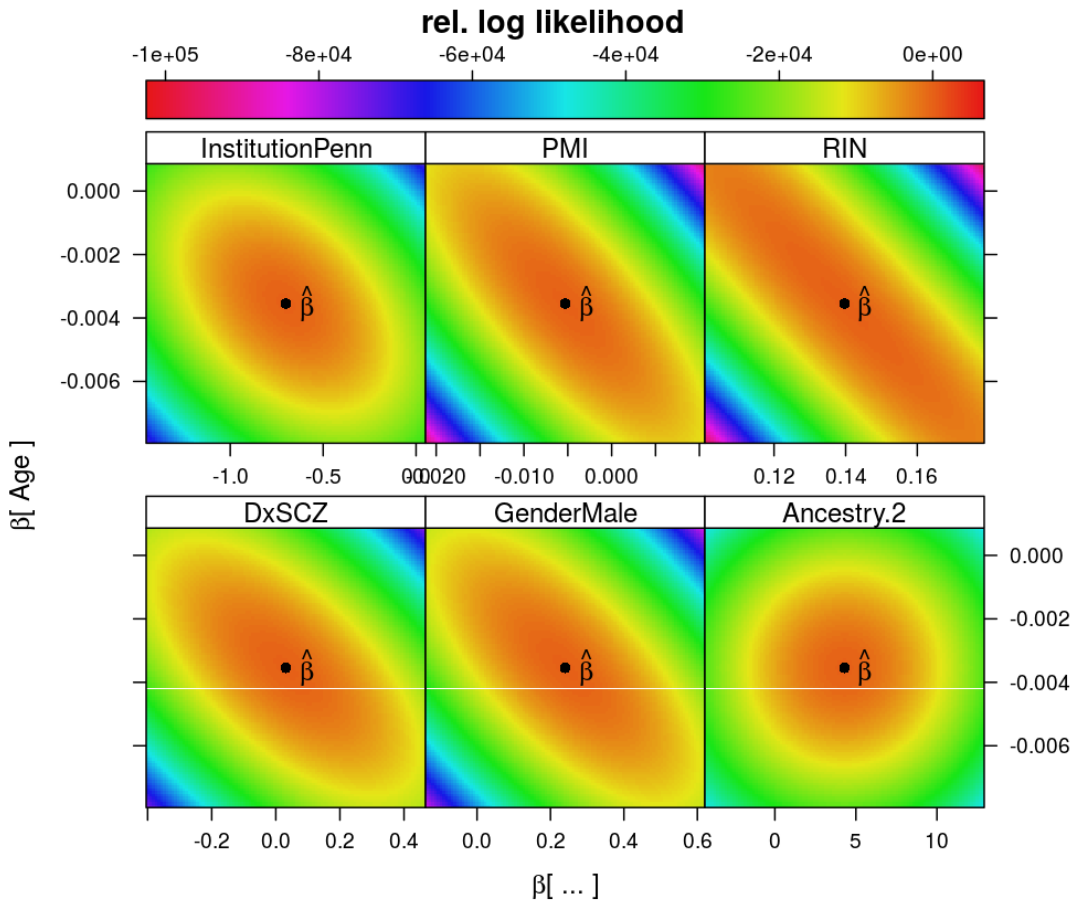
y	$x_{\cdot 1}$	$x_{\cdot 2}$	$x_{\cdot 3}$
y_1	x_{11}	x_{12}	x_{13}
$\vdots$	$\vdots$	$\vdots$	$\vdots$
y_m	x_{m1}	x_{m2}	x_{m3}



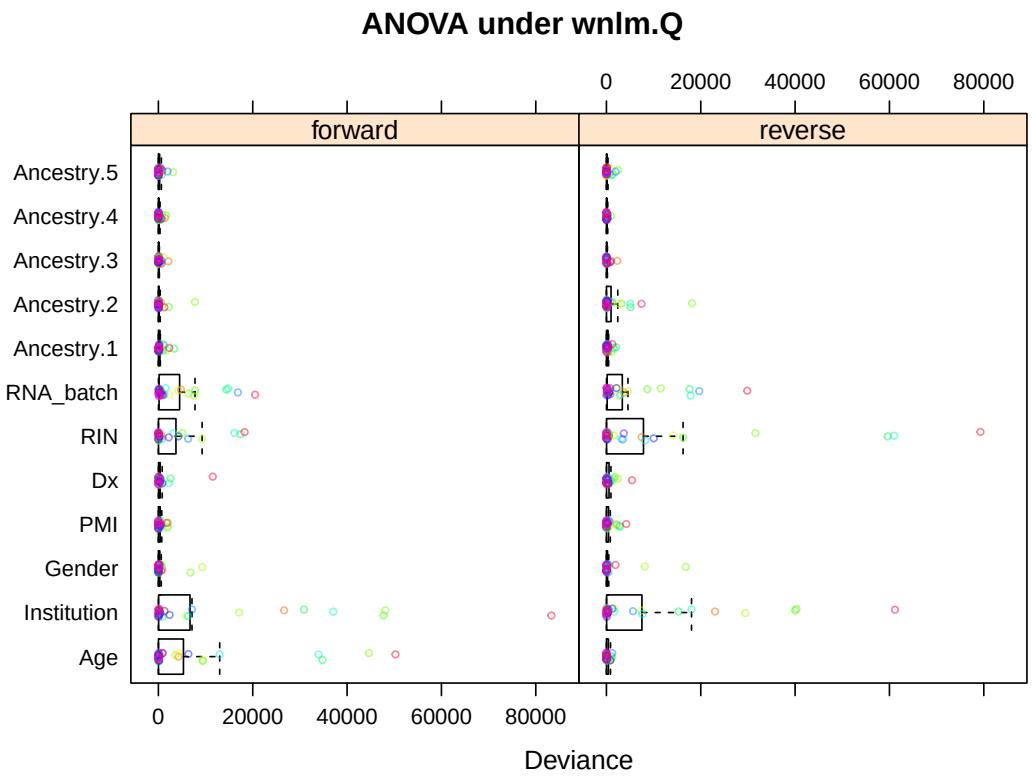
The Common Mind data



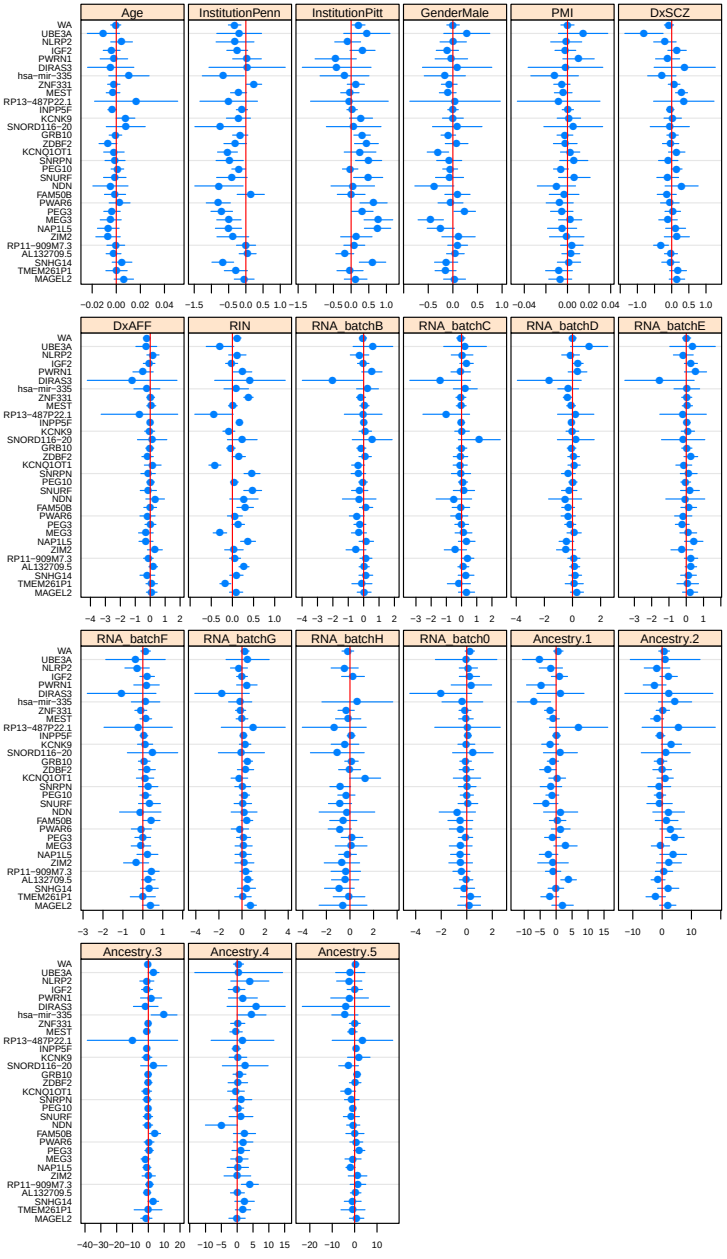
Consequence: poor identifiability



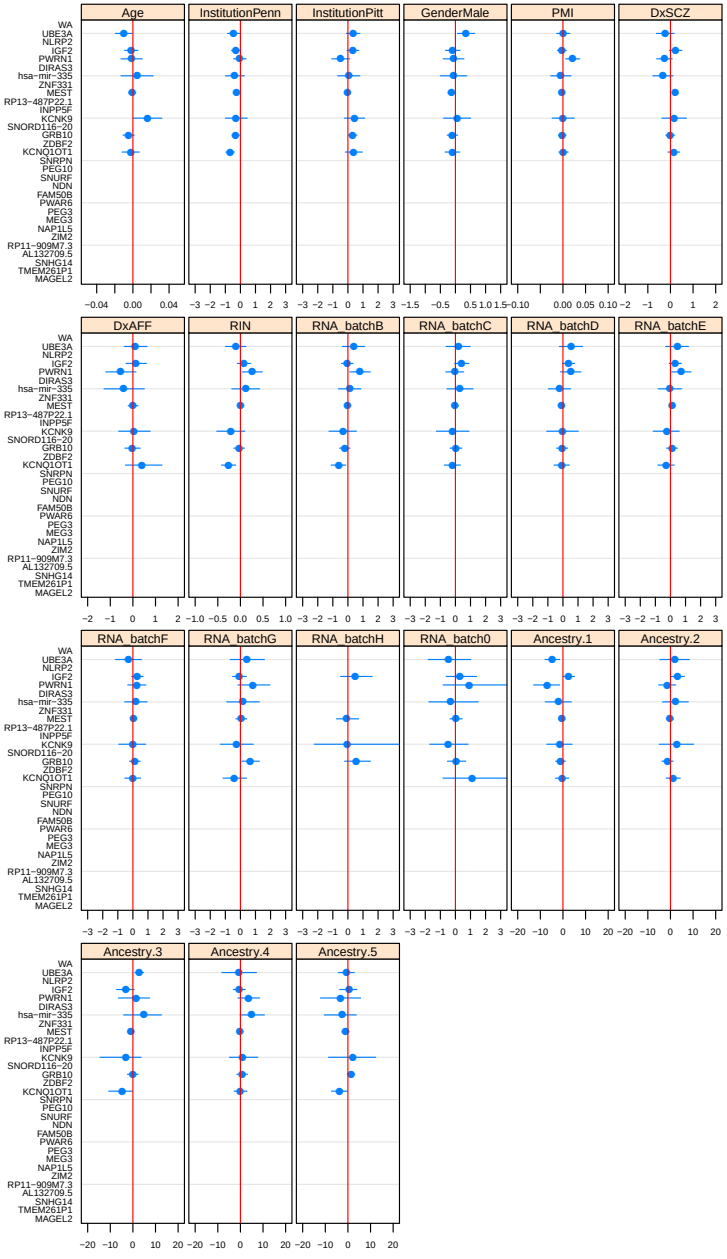
Consequence: ANOVA is inconclusive



99 % CI for β under wnlm.Q

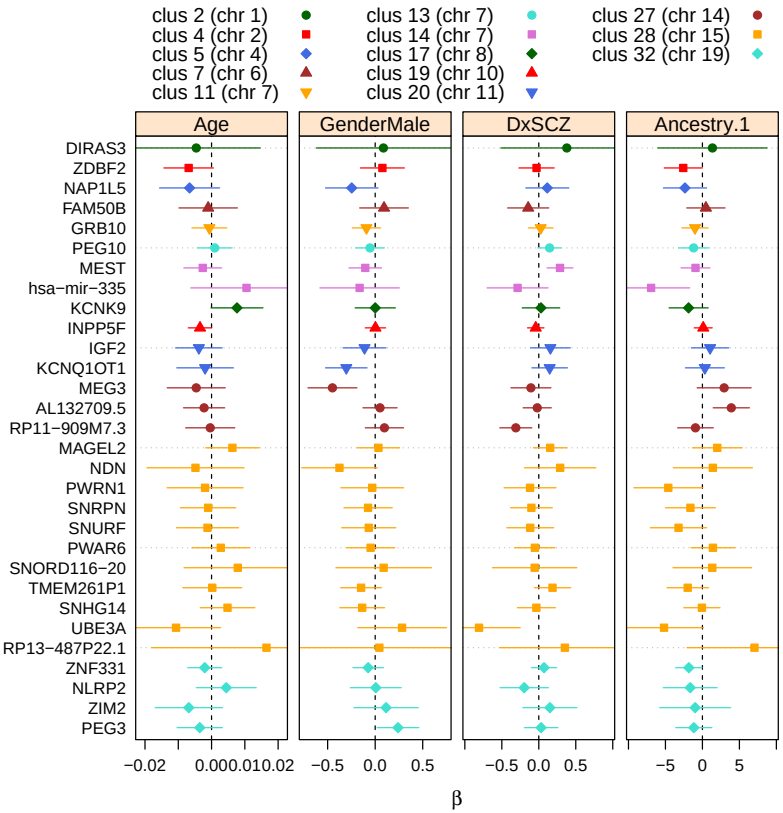


99 % CI for β under logi.S



The main results

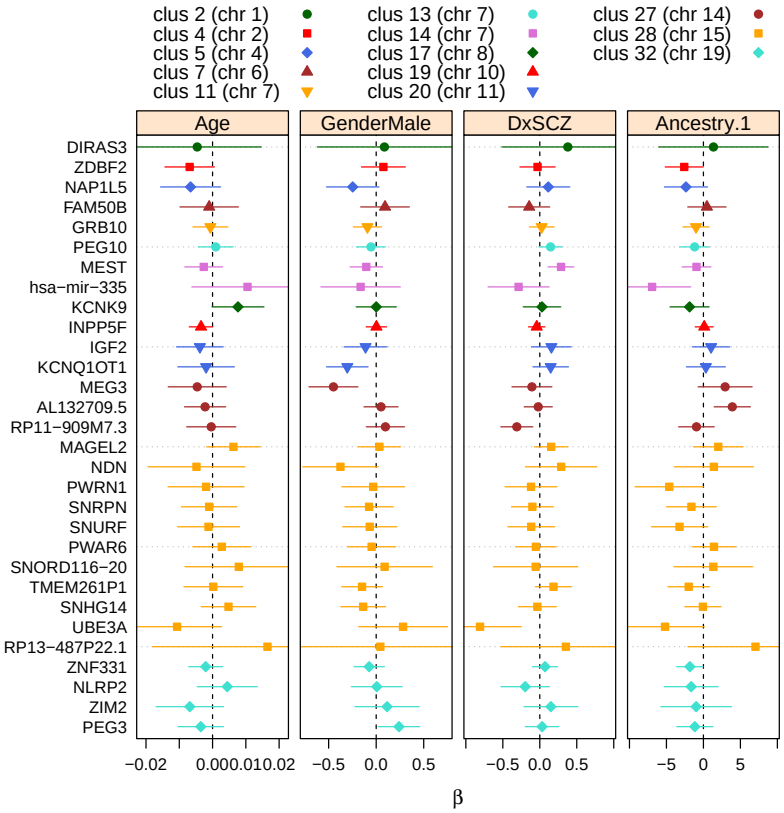
biological effects



model: wnlm.Q

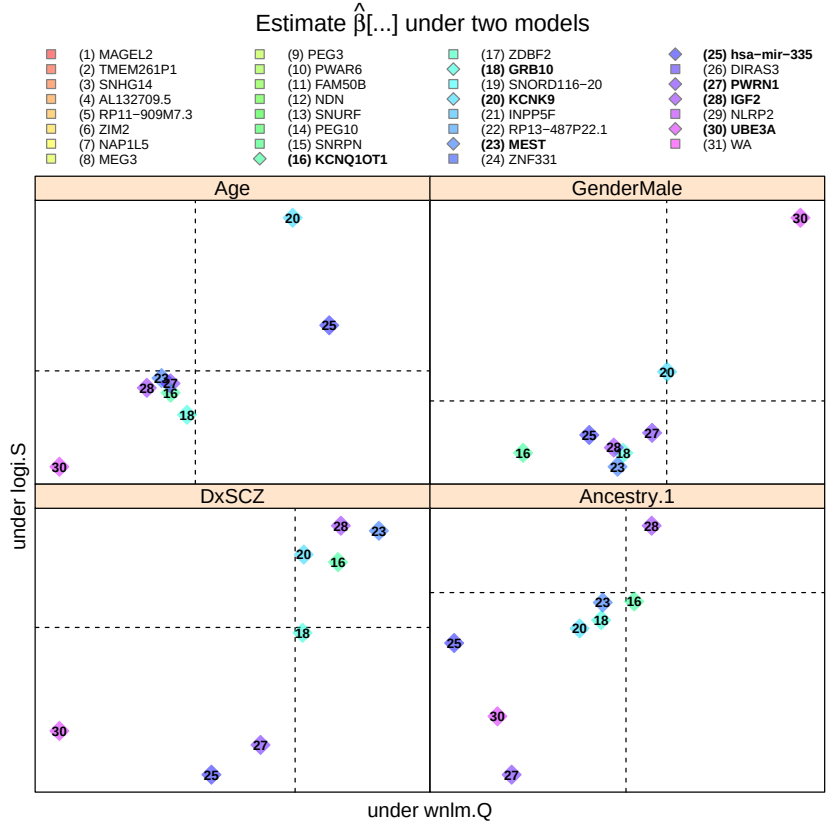
The main results

biological effects

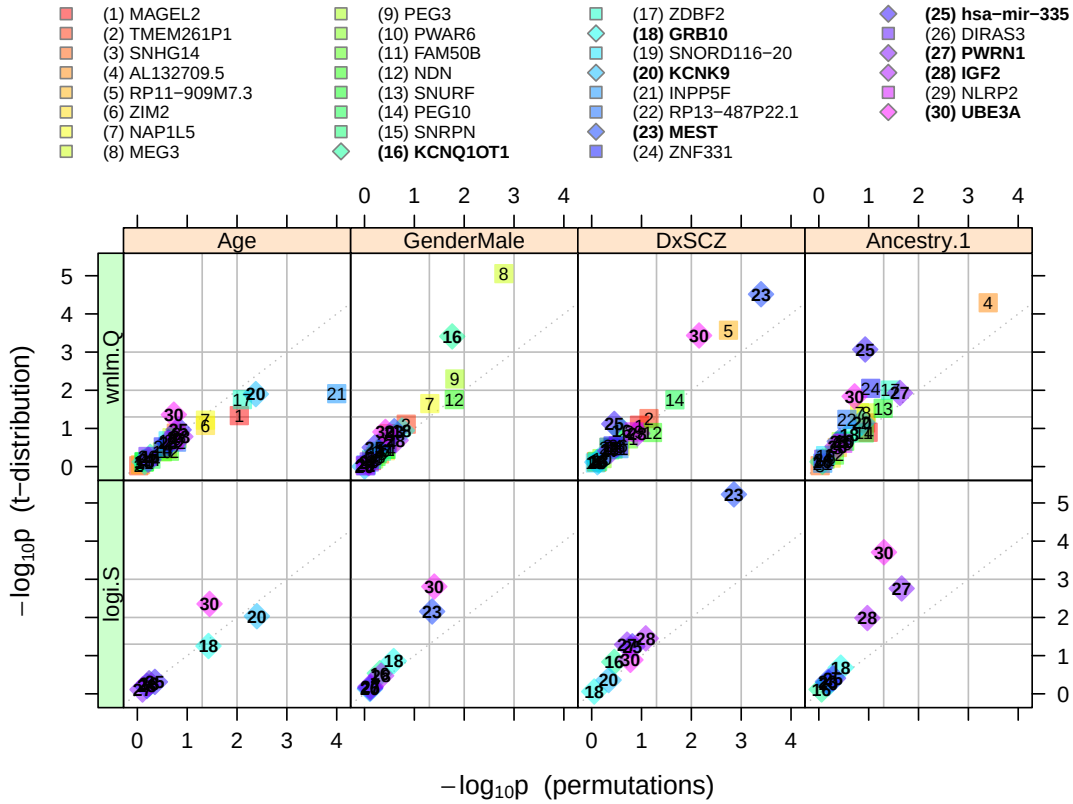


model: wnlm.Q

agreement between models



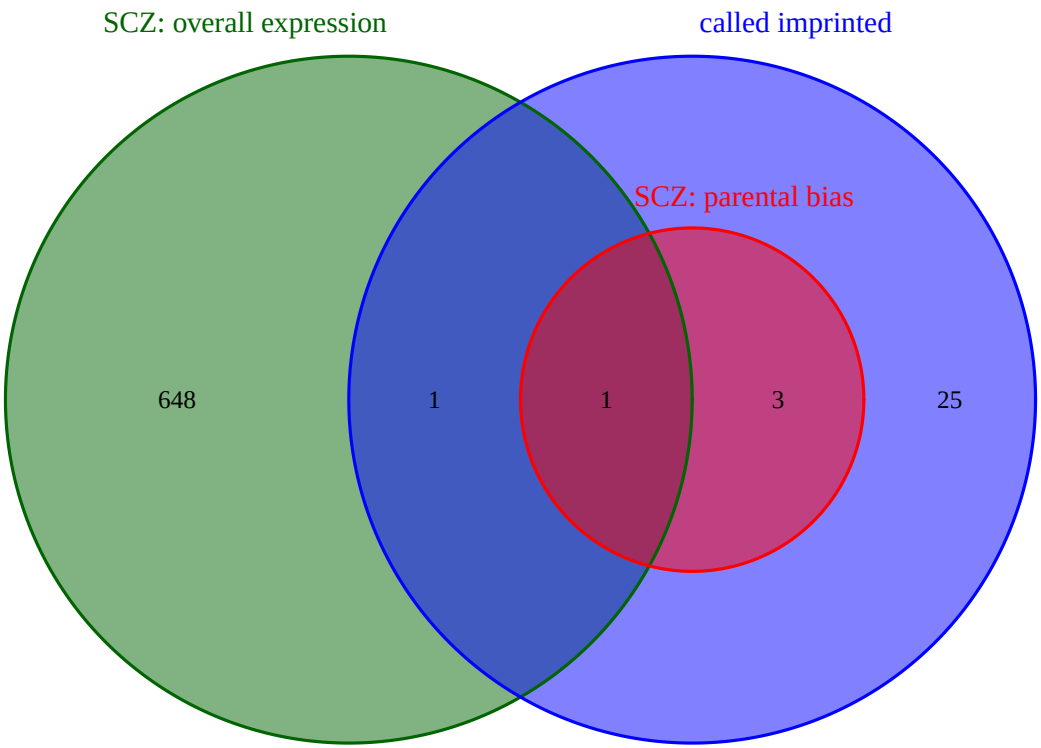
p-values for $\mathcal{H}_0$: no dependence



Affected genes ($\mathcal{H}_0$ rejected)

Gene	Gene type	Chr	Coefficient	Known phenotype
ZDBF2	protein coding	2	Age, Ancestry.1	
NAP1L5	protein coding	4	GenderMale	
PEG10	protein coding	7	DxSCZ	
MEST	protein coding	7	DxSCZ	Silver-Russell syndrome
KCNK9	protein coding	8	Age	Birk-Barel mental retardation dysmorphism syndrome
INPP5F	protein coding	10	Age	cell motility; endocytic recycling
KCNQ1OT1	antisense	11	GenderMale	Beckwith-Wiedemann syn.; Isol. hemihyperplasia
MEG3	lincRNA	14	GenderMale	Mat/pat 14q32.2 hypermeth/microdel syndrome
RP11-909M7.3	lincRNA	14	DxSCZ	
AL132709.5	miRNA	14	Ancestry.1	
MAGEL2	protein coding	15	Age	Prader-Willi syn.; Schaaf-Yang syn.; Arthrogryposis
NDN	protein coding	15	GenderMale	Prader-Willi syndrome
PWRN1	lincRNA	15	Ancestry.1	Prader-Willi syndrome
UBE3A	protein coding	15	DxSCZ	Prader-Willi syn.; Angelman syn.; circadian rhythm
PEG3	protein coding	19	GenderMale	

Comparison to overall expression analysis*



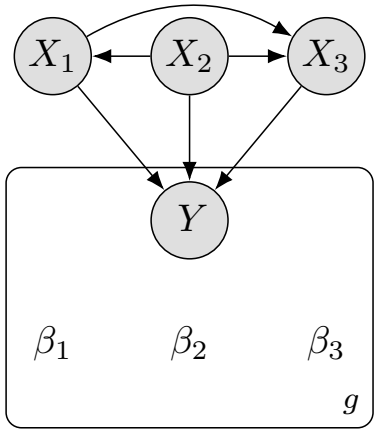
*Fromer et al 2016

Summary of results

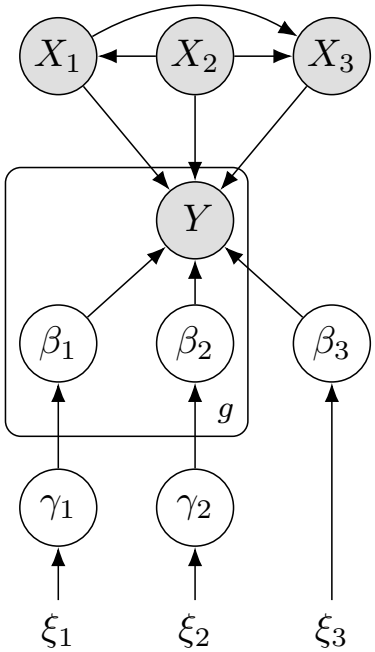
1. $\approx 1\%$ of genes imprinted in the human brain
2. age, gender and genetics regulate parental bias
3. bias of some genes is linked to schizophrenia
4. our statistical models have limitations

Improving and extending statistical approach

present: "flat"



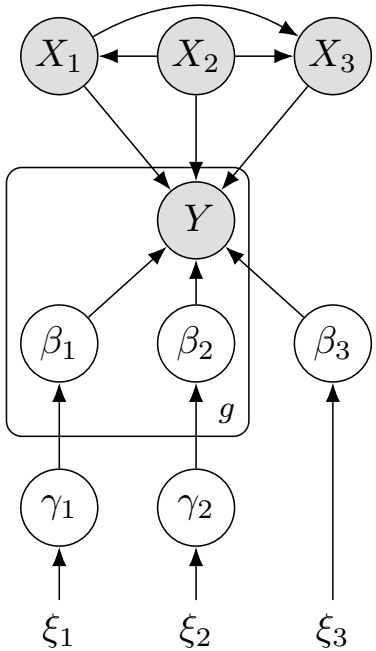
proposed: hierarch.



- more power
  - borrowing of strength
  - shared parameters
- more realism
  - interactions
- more answers
  - tissue specificity
  - DNA methylation

Improving and extending statistical approach

proposed: hierarch.



- more power
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Thank you

Chess lab

- Andy Chess
- Chaggai Rosenbluh
- Eva Xia
- Mehaa Bajaj