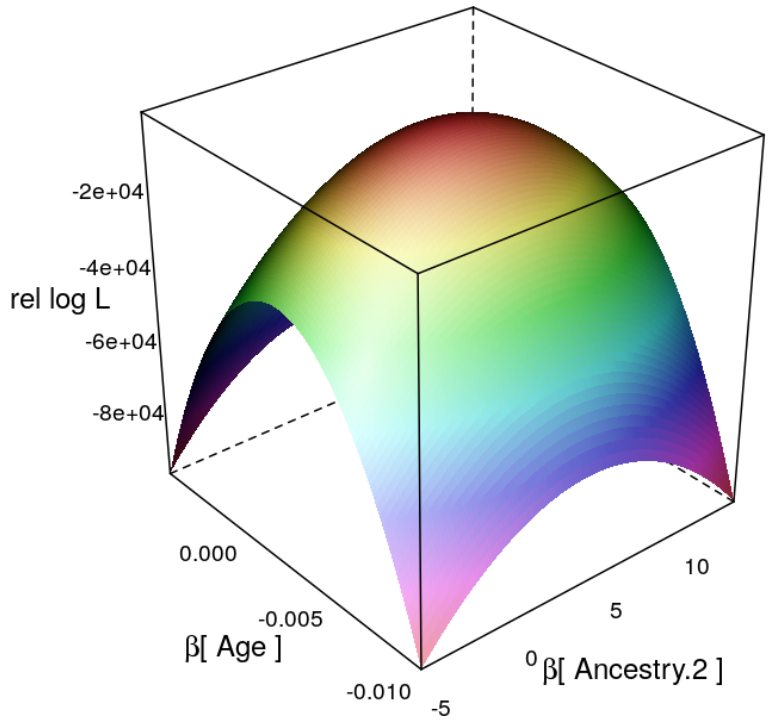
Imprinting, schizophrenia, and aging

investigated with mixed models and CommonMind data

Attila Gulyás-Kovács, Chess lab



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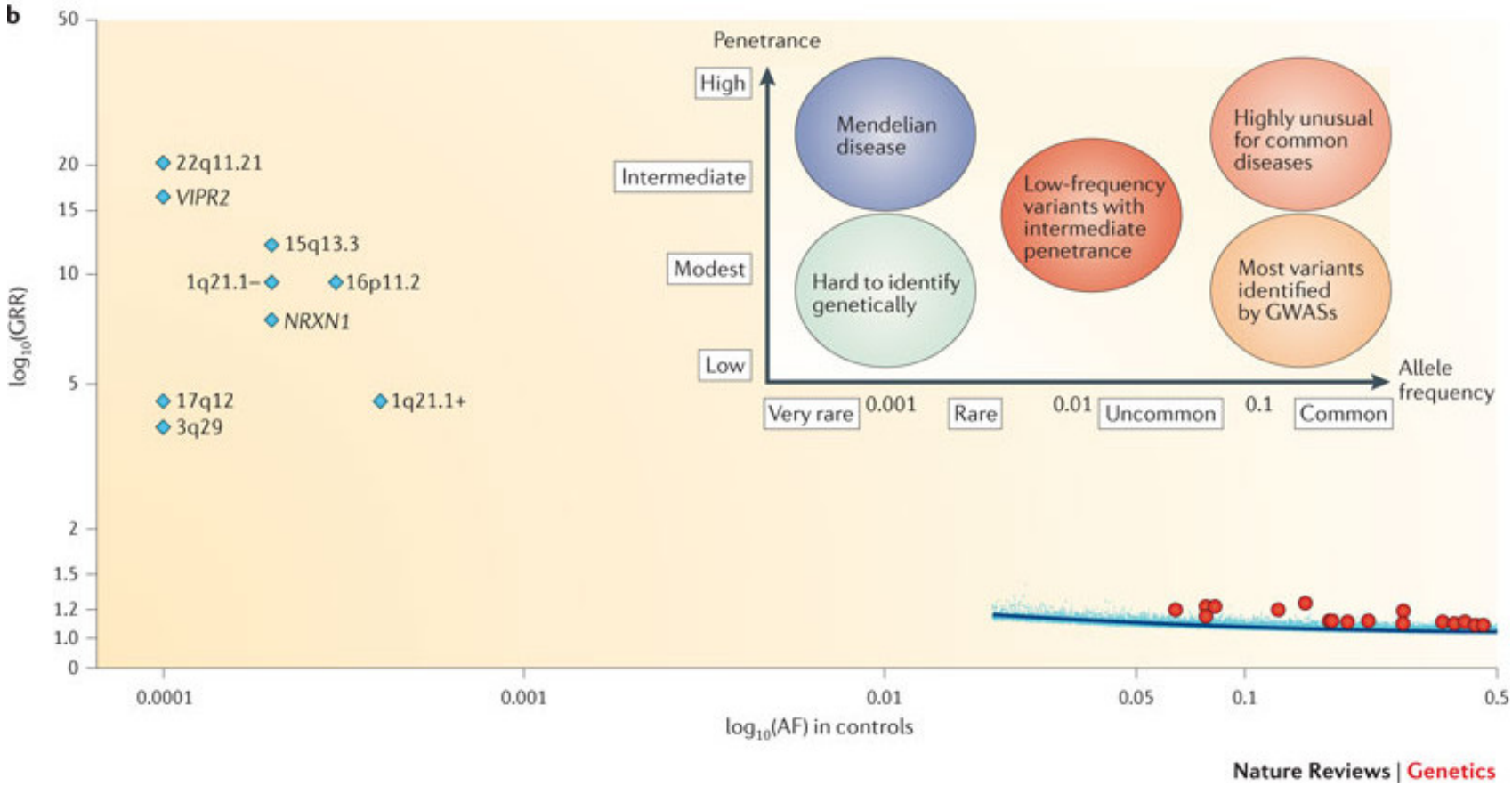
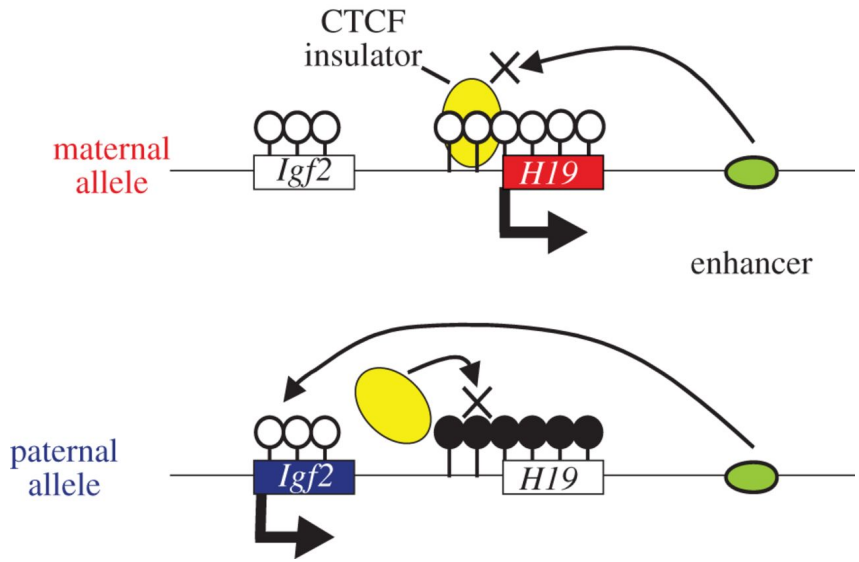
Schizophrenia: complex genetic architecture



Imprinting and allelic bias

1. roles
   - psychiatric?
   - mother–child interaction
   - neurodevelopmental
2. variation: age, tissue



Renfree et al 2012 Philos Trans R Soc Lond B

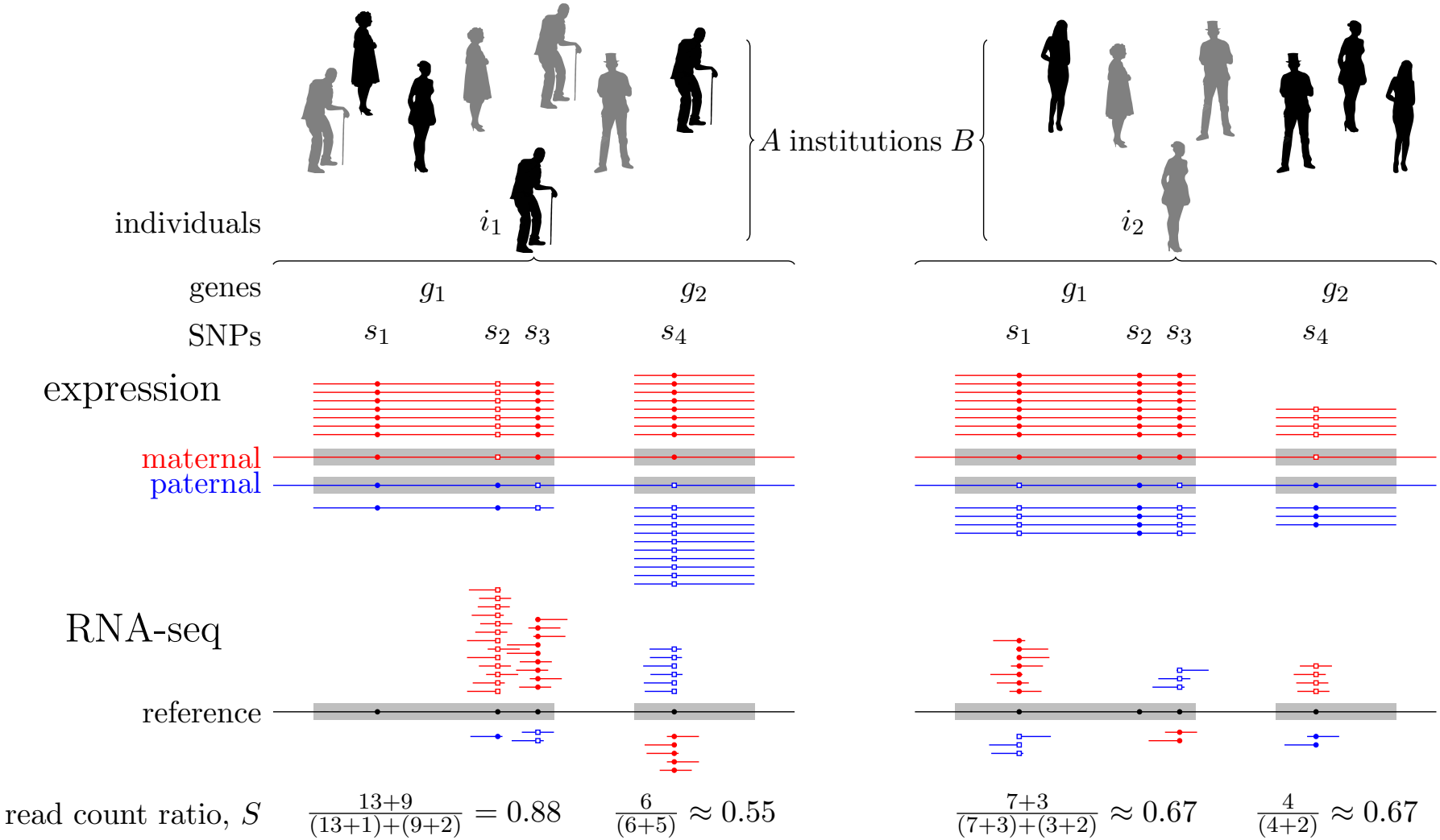
Our *previous* work

- CommonMind Consortium data
- 30 imprinted genes in DLPFC, some novel
- found allelic bias to depend on SCZ, age
  - genes varied
  - weak statistical support
- mixed models: more power
- found allelic bias to depend on age but not SCZ
  - genes varied

Our *revised* work

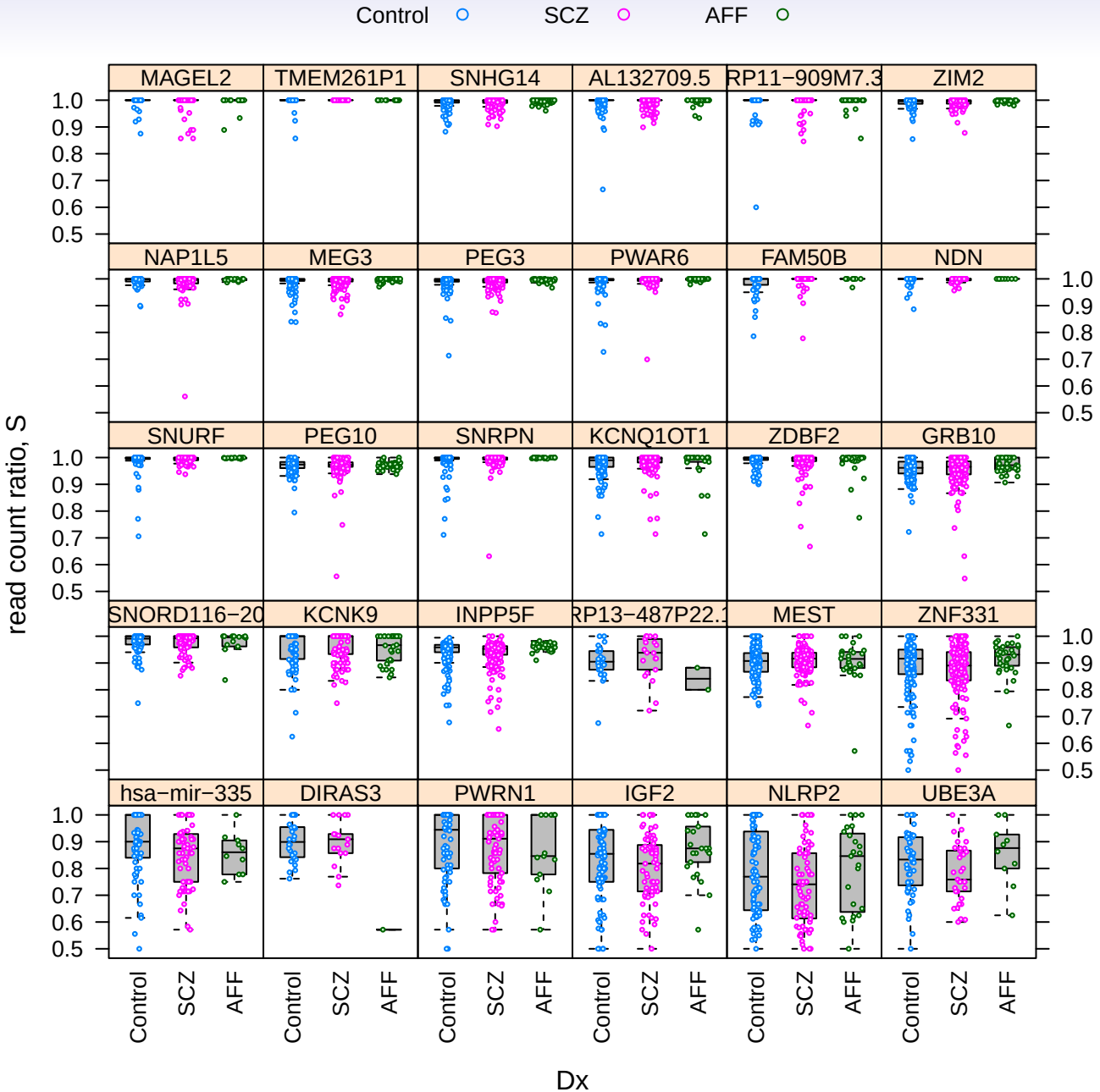
- CommonMind Consortium data
- 30 imprinted genes in DLPFC, some novel
- found allelic bias to depend on SCZ, age
  - genes varied
  - weak statistical support
- mixed models: more power
- found allelic bias to depend on age but not SCZ
  - genes varied

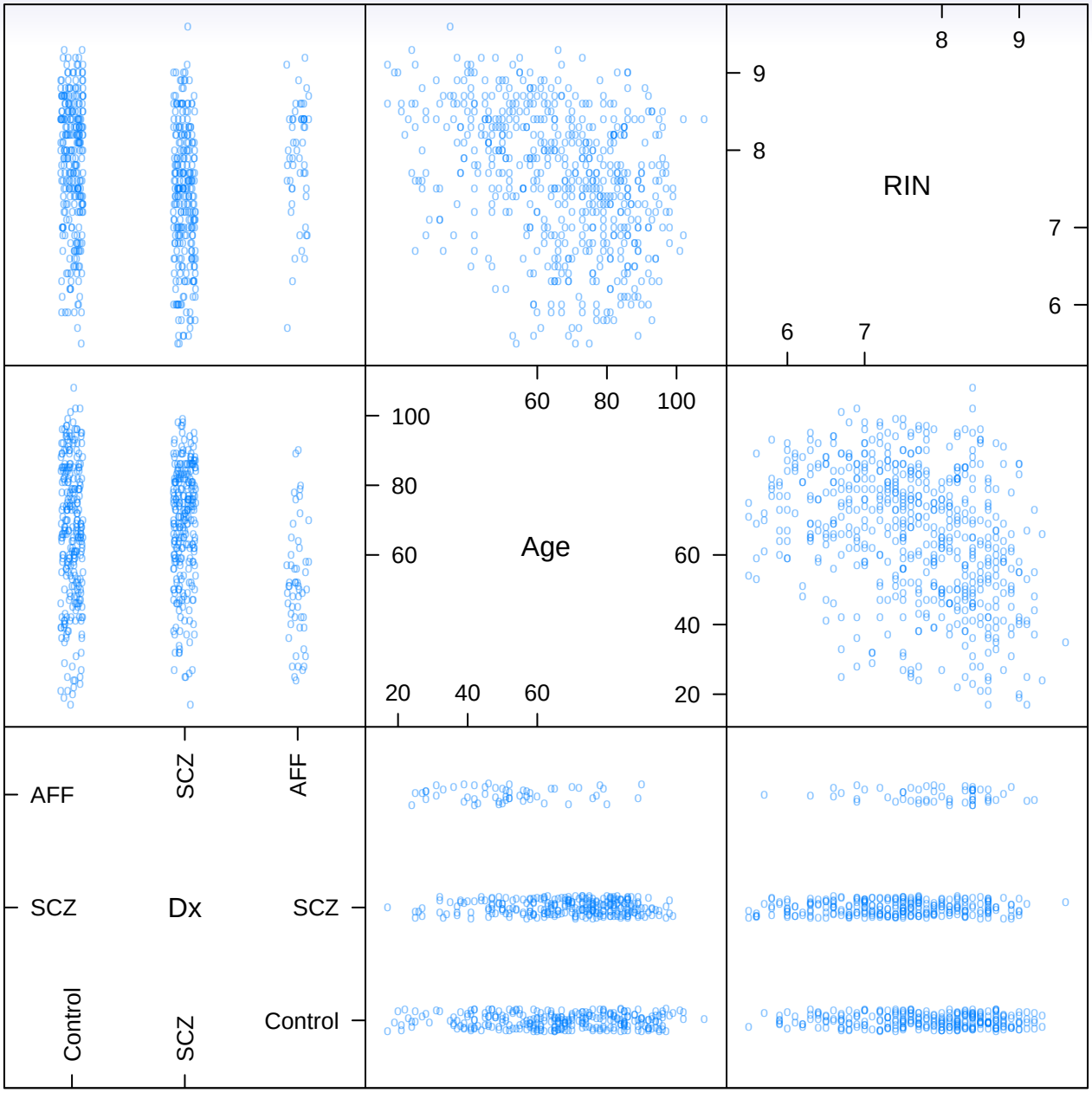
Read count ratio measures allelic expression bias

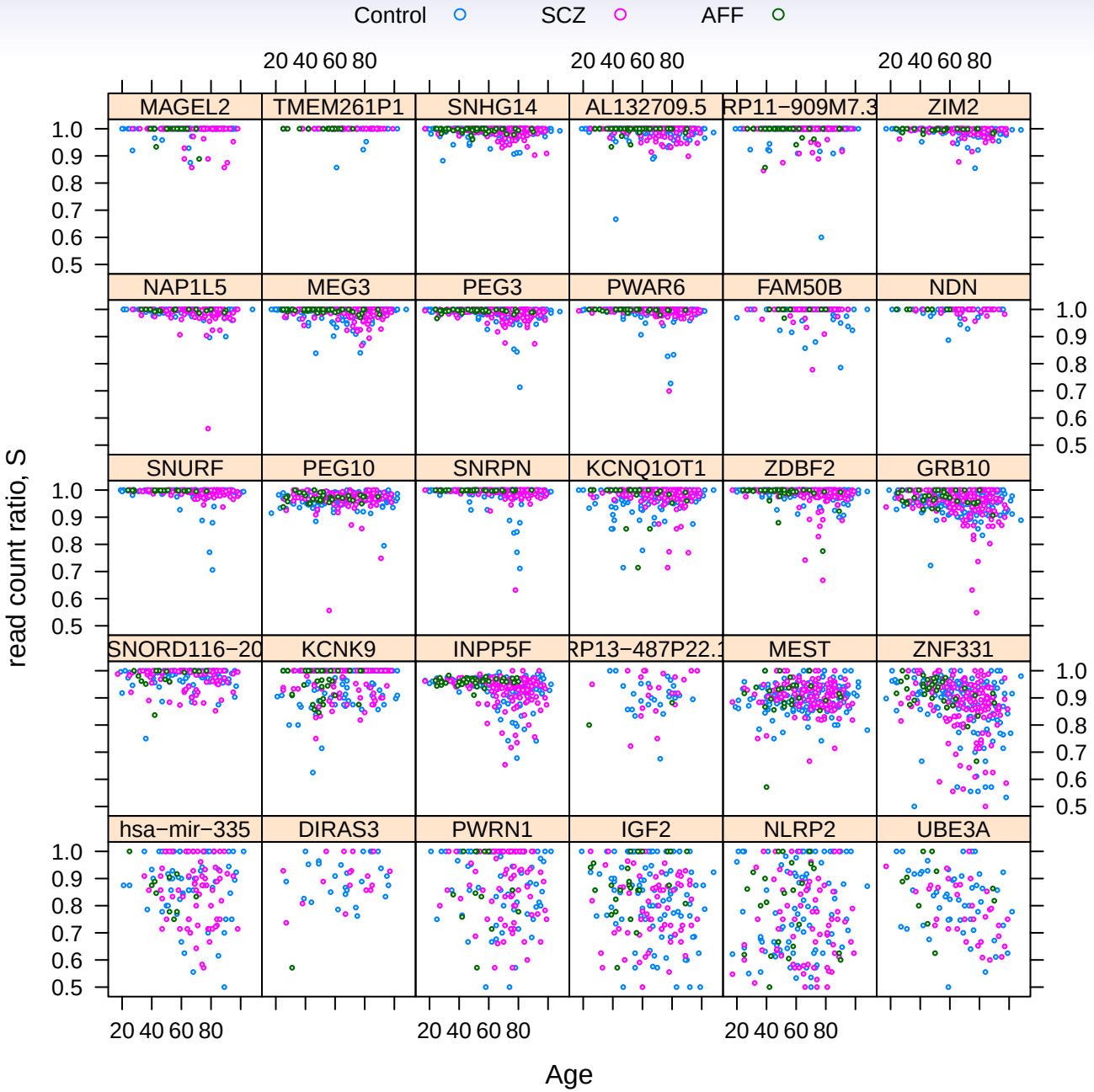


The data

	read count ratios			explanatory variables			
i	Y_1	...	Y_{30}	X_1	X_2	...	X_{12}
Individual	**MAGEL2**	...	**UBE3A**	**Dx**	**Age**	...	**RIN**
1	NA	...	NA	AFF	42	...	6.90
2	1.00	...	NA	AFF	58	...	7.00
3	NA	...	0.89	AFF	28	...	6.90
⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮
576	0.97	...	NA	Control	42	...	8.50
577	1.00	...	NA	SCZ	27	...	7.50
578	1.00	...	NA	Control	57	...	8.60
579	1.00	...	1.00	Control	28	...	7.70


Control
SCZ
AFF
MAGEL2
TMEM261P1
SNHG14
AL132709.5
RP11−909M7.3
ZIM2
NAP1L5
MEG3
PEG3
PWAR6
FAM50B
NDN
SNURF
PEG10
SNRPN
KCNQ1OT1
ZDBF2
GRB10
SNORD116−20
KCNK9
INPP5F
RP13−487P22.1
MEST
ZNF331
hsa−mir−335
DIRAS3
PWRN1
IGF2
NLRP2
UBE3A
read count ratio, S
Dx


RIN
Age
Dx
AFF
SCZ
Control


Control
SCZ
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MAGEL2
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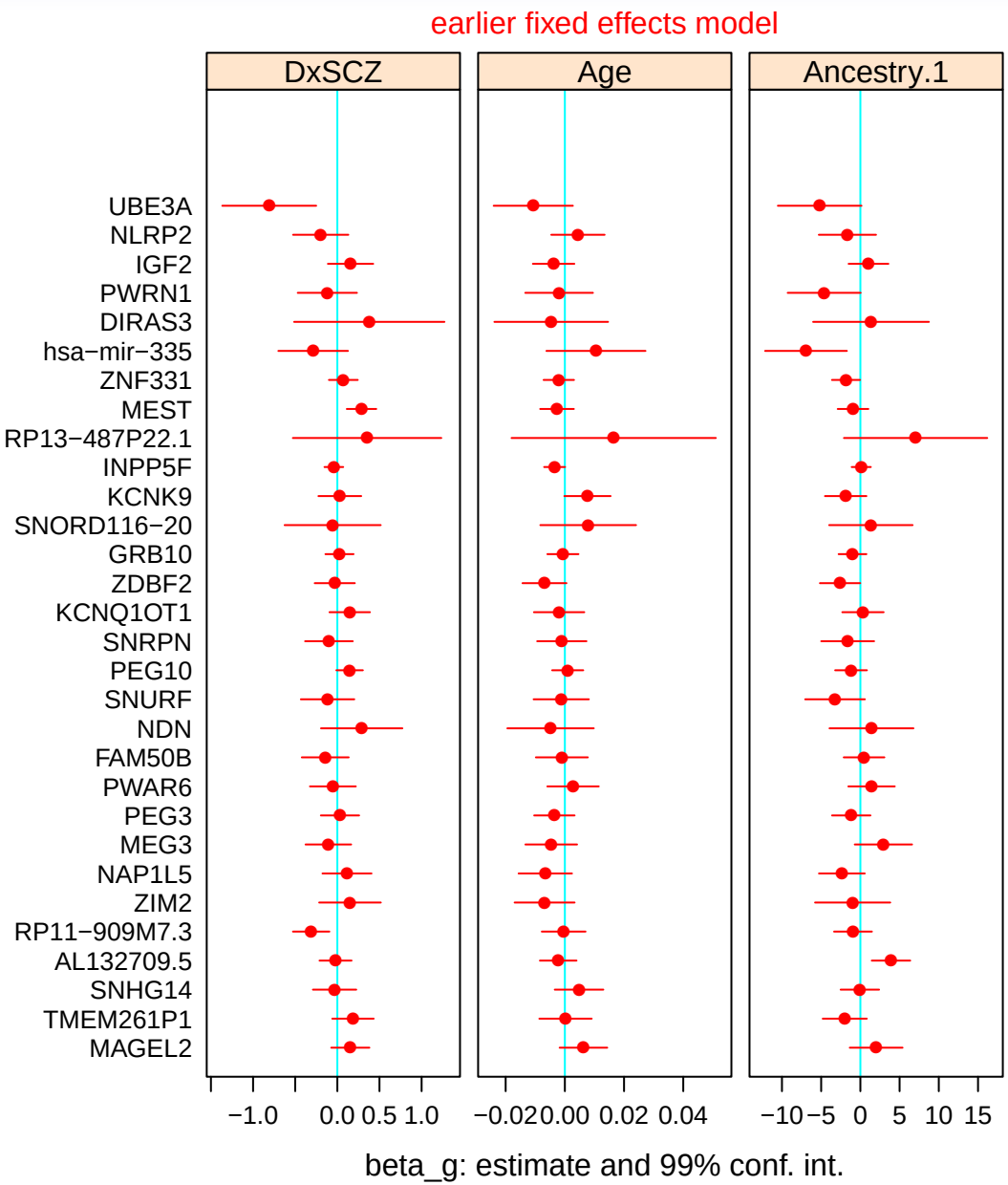
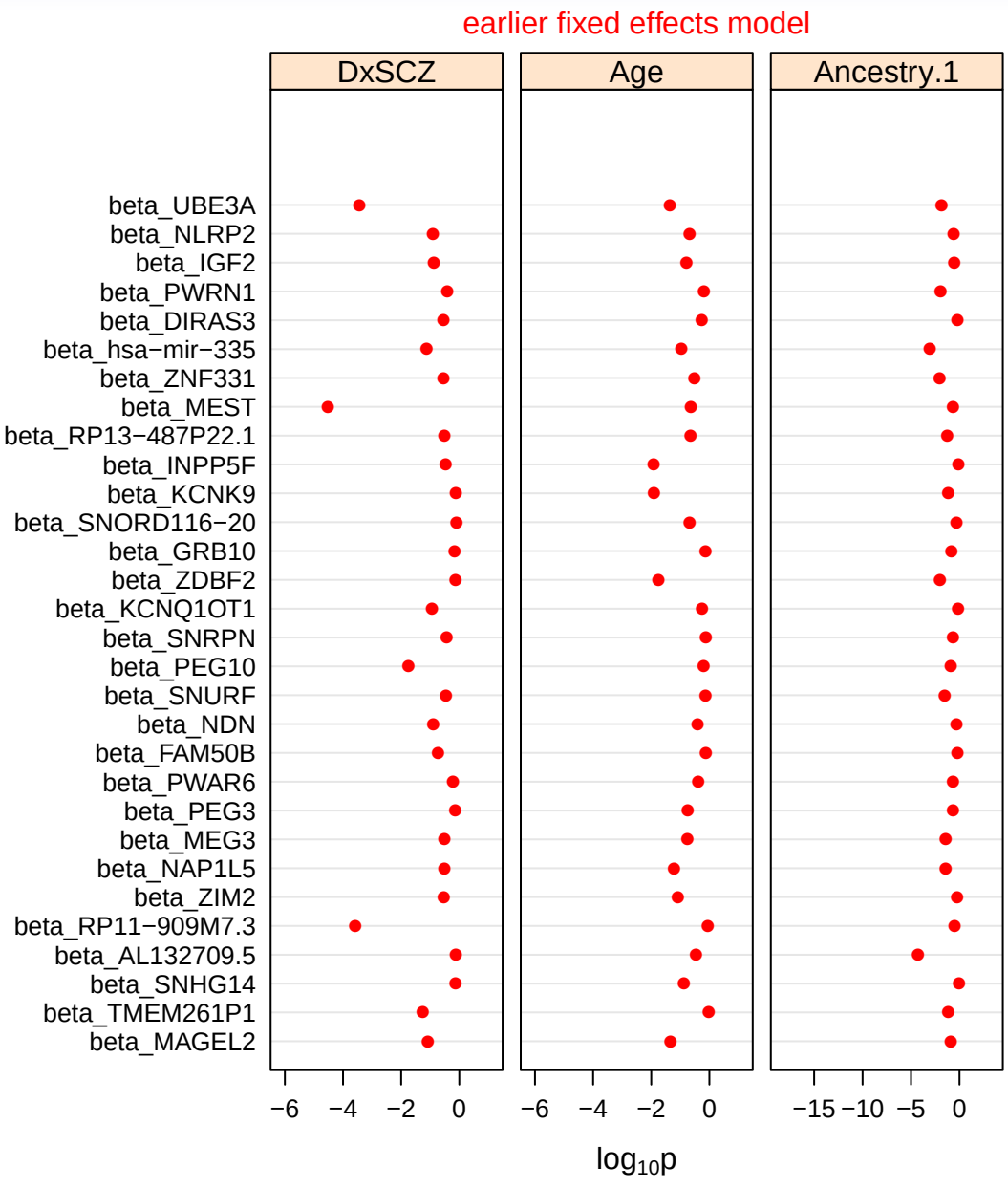
RP11−909M7.3
ZIM2
NAP1L5
MEG3
PEG3
PWAR6
FAM50B
NDN
SNURF
PEG10
SNRPN
KCNQ1OT1
ZDBF2
GRB10
SNORD116−20
KCNK9
INPP5F
RP13−487P22.1
MEST
ZNF331
hsa−mir−335
DIRAS3
PWRN1
IGF2
NLRP2
UBE3A
20 40 60 80
1.0
0.9
0.8
0.7
0.6
0.5
read count ratio, S
Age


earlier fixed effects model
DxSCZ
Age
Ancestry.1
UBE3A
NLRP2
IGF2
PWRN1
DIRAS3
hsa−mir−335
ZNF331
MEST
RP13−487P22.1
INPP5F
KCNK9
SNORD116−20
GRB10
ZDBF2
KCNQ1OT1
SNRPN
PEG10
SNURF
NDN
FAM50B
PWAR6
PEG3
MEG3
NAP1L5
ZIM2
RP11−909M7.3
AL132709.5
SNHG14
TMEM261P1
MAGEL2
−1.0 0.0 0.5 1.0
−0.02 0.00 0.02 0.04
−10 −5 0 5 10 15
beta_g: estimate and 99% conf. int.


earlier fixed effects model
DxSCZ
Age
Ancestry.1
beta_UBE3A
beta_NLRP2
beta_IGF2
beta_PWRN1
beta_DIRAS3
beta_hsa−mir−335
beta_ZNF331
beta_MEST
beta_RP13−487P22.1
beta_INPP5F
beta_KCNK9
beta_SNORD116−20
beta_GRB10
beta_ZDBF2
beta_KCNQ1OT1
beta_SNRPN
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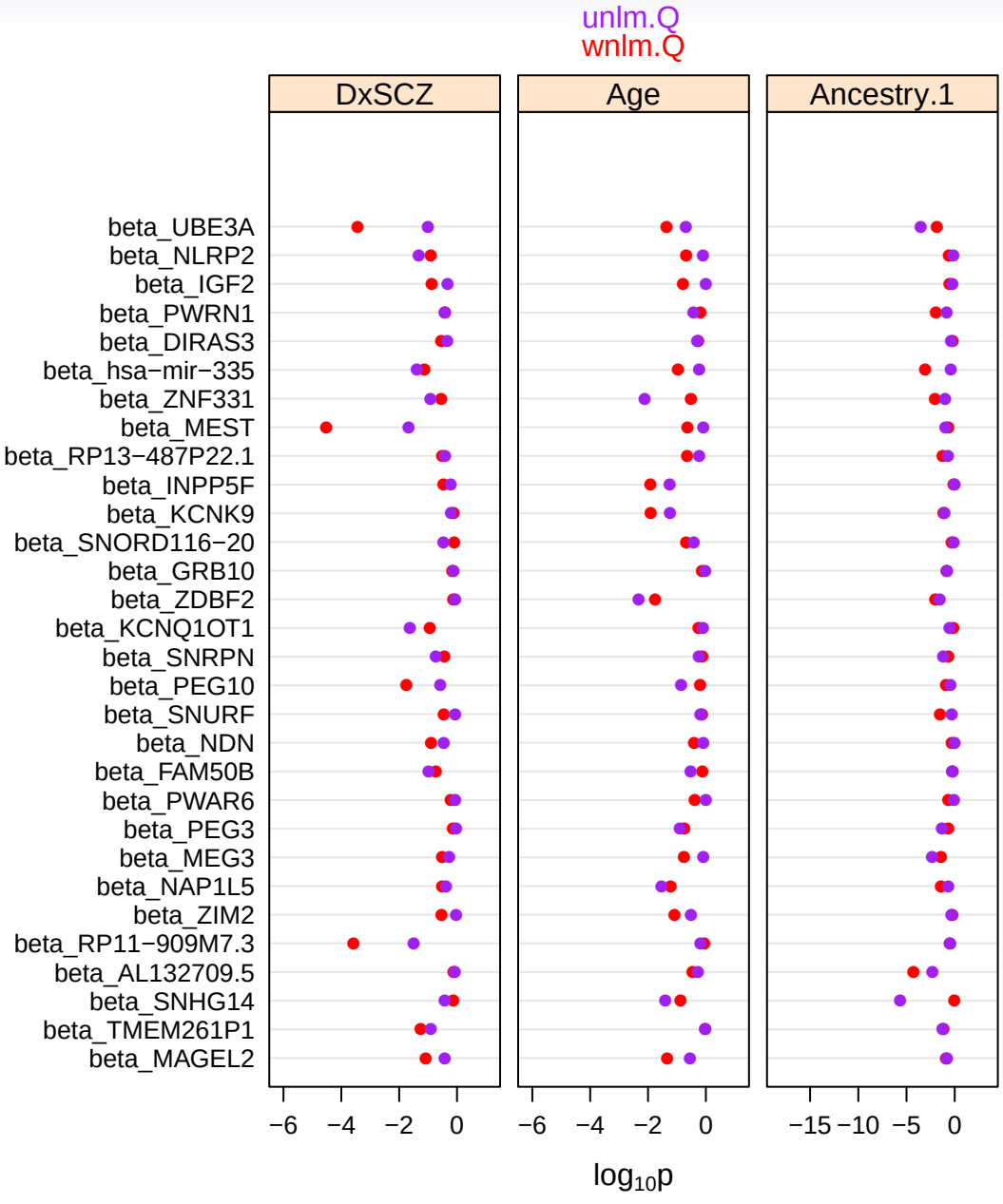
beta_PWAR6
beta_PEG3
beta_MEG3
beta_NAP1L5
beta_ZIM2
beta_RP11−909M7.3
beta_AL132709.5
beta_SNHG14
beta_TMEM261P1
beta_MAGEL2
−6 −4 −2 0
−6 −4 −2 0
−15 −10 −5 0
log10p


unlm.Q
wnlm.Q
DxSCZ
Age
Ancestry.1
beta_UBE3A
beta_NLRP2
beta_IGF2
beta_PWRN1
beta_DIRAS3
beta_hsa−mir−335
beta_ZNF331
beta_MEST
beta_RP13−487P22.1
beta_INPP5F
beta_KCNK9
beta_SNORD116−20
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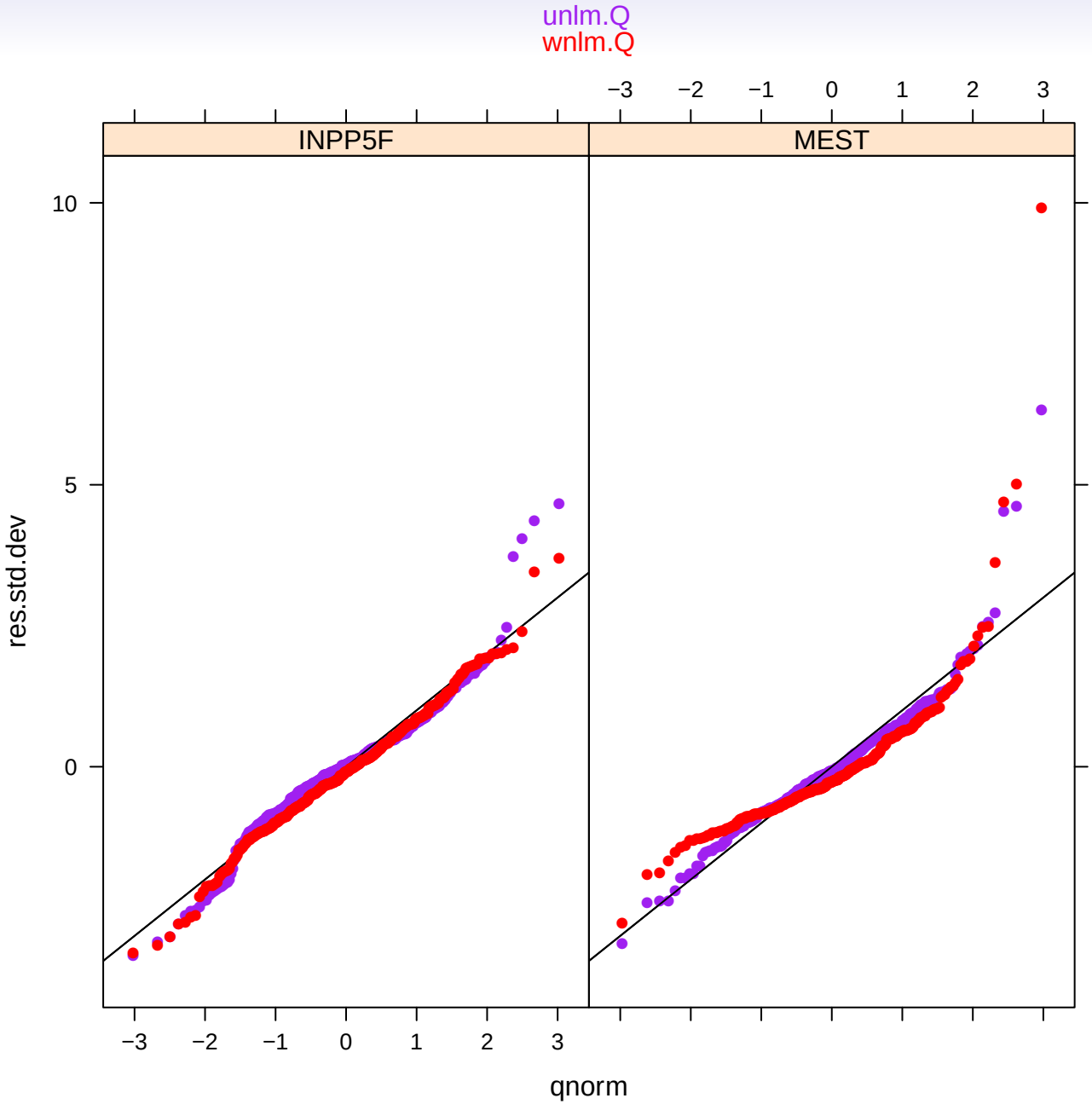
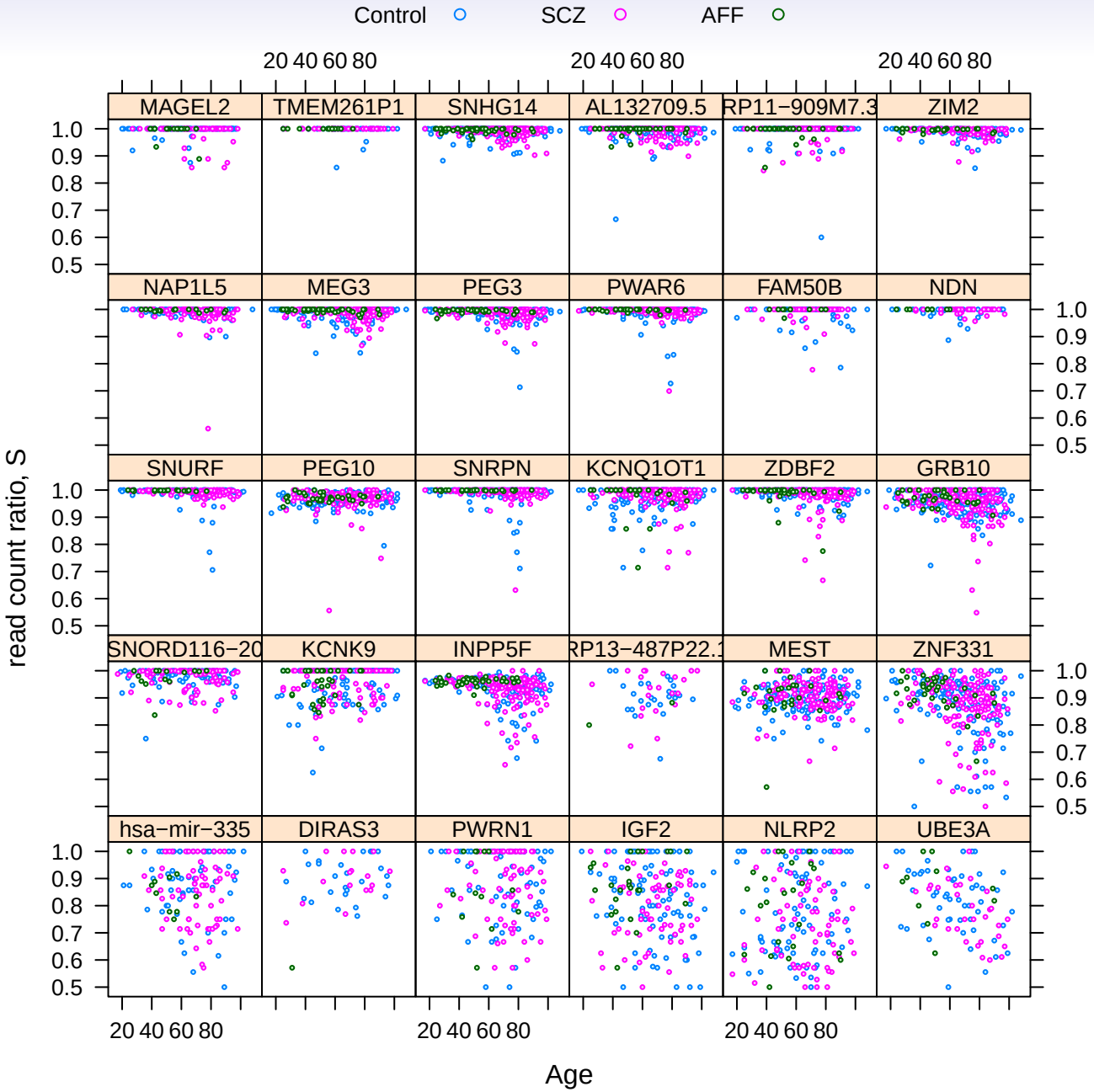
beta_NAP1L5
beta_ZIM2
beta_RP11−909M7.3
beta_AL132709.5
beta_SNHG14
beta_TMEM261P1
beta_MAGEL2
−6 −4 −2 0
−6 −4 −2 0
−15 −10 −5 0
log10p


unlm.Q
wnlm.Q
INPP5F
MEST
res.std.dev
qnorm
10
5
0
−3
−2
−1
0
1
2
3


Control
SCZ
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MAGEL2
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AL132709.5
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ZIM2
NAP1L5
MEG3
PEG3
PWAR6
FAM50B
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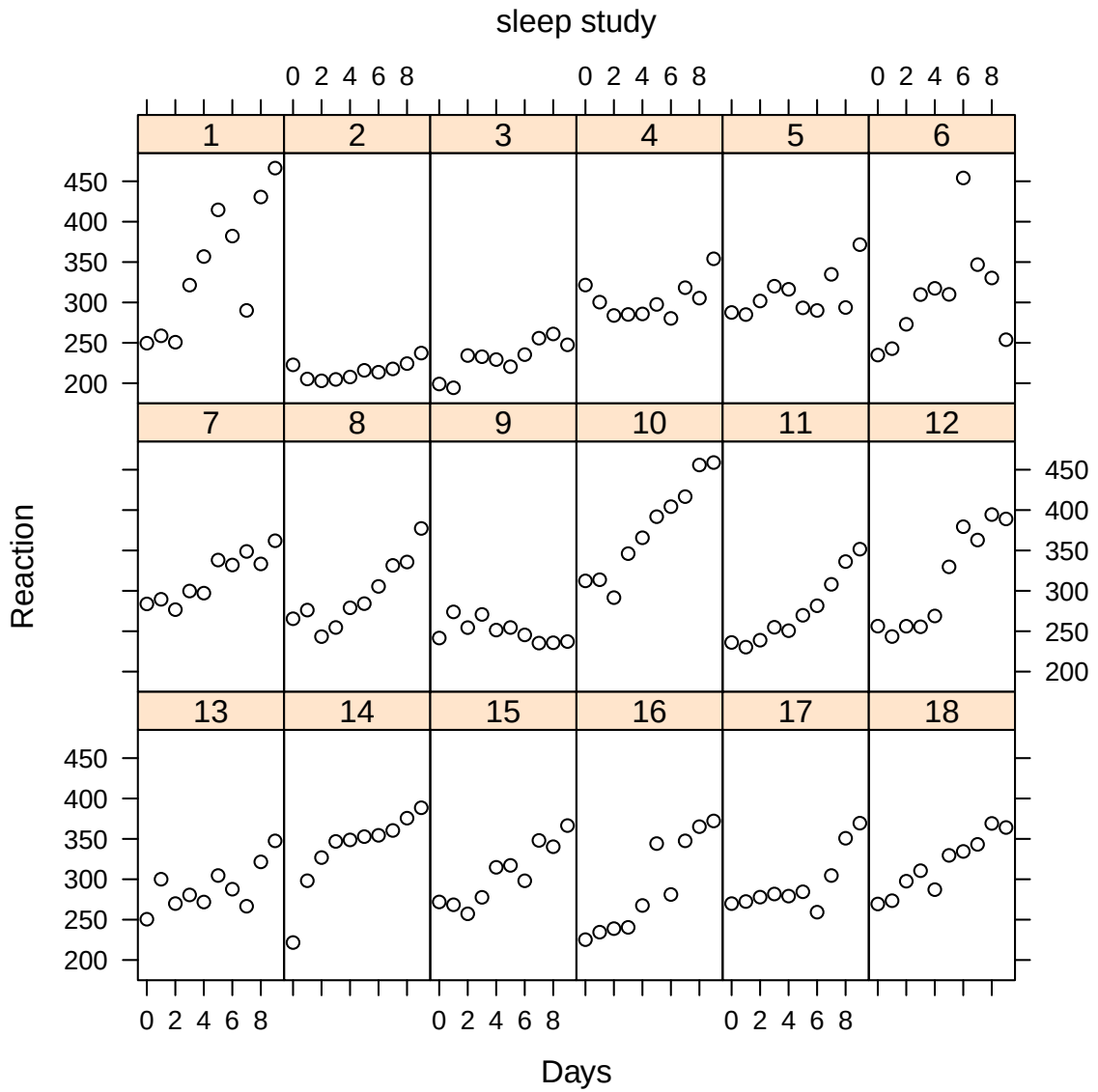
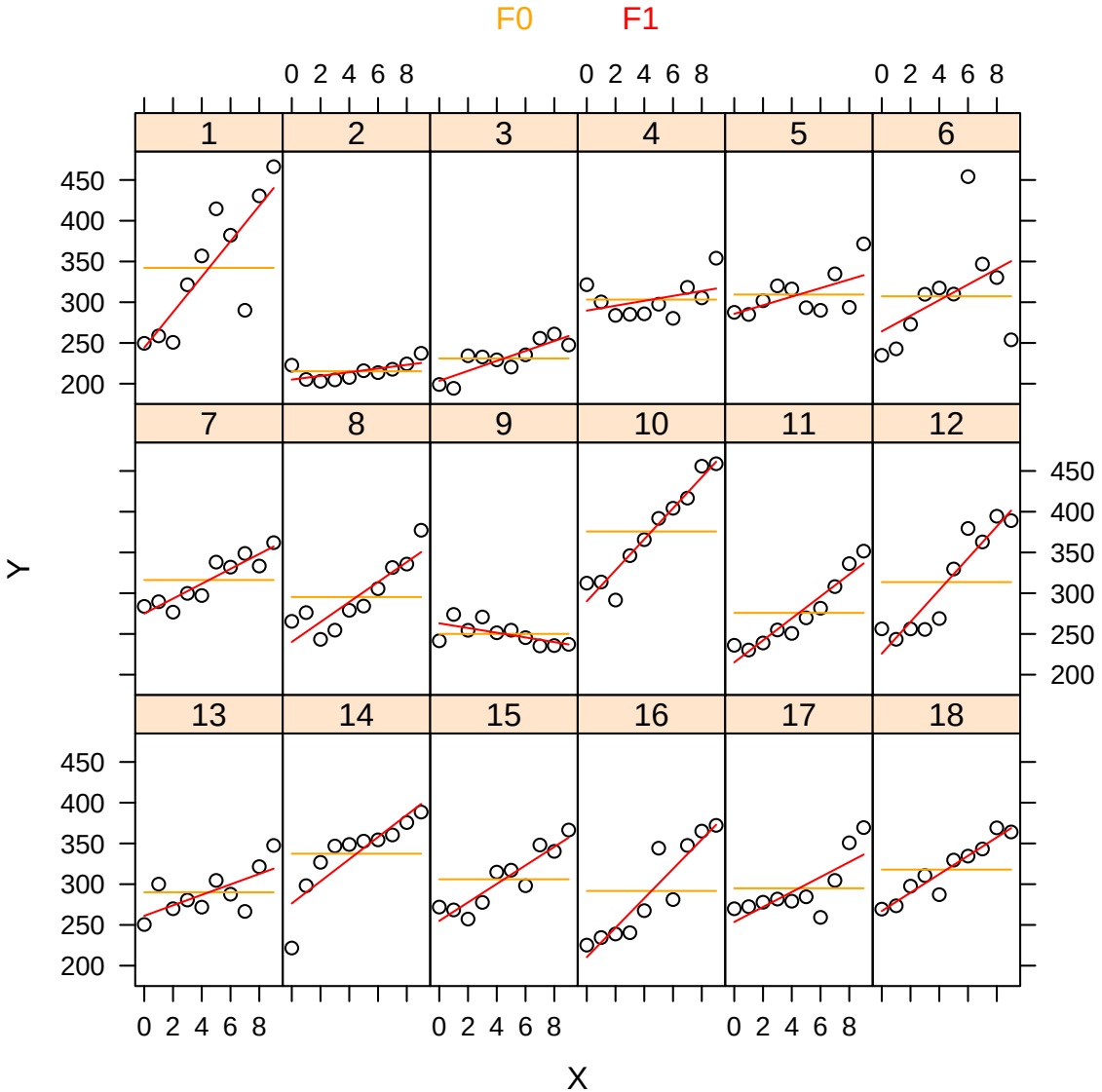
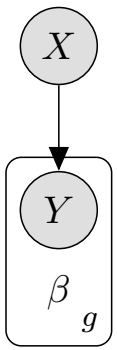
PEG10
SNRPN
KCNQ1OT1
ZDBF2
GRB10
SNORD116−20
KCNK9
INPP5F
RP13−487P22.1
MEST
ZNF331
hsa−mir−335
DIRAS3
PWRN1
IGF2
NLRP2
UBE3A
20 40 60 80
1.0
0.9
0.8
0.7
0.6
0.5
read count ratio, S
Age


sleep study
Reaction
Days
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
0 2 4 6 8
200
250
300
350
400
450



fixed

F1



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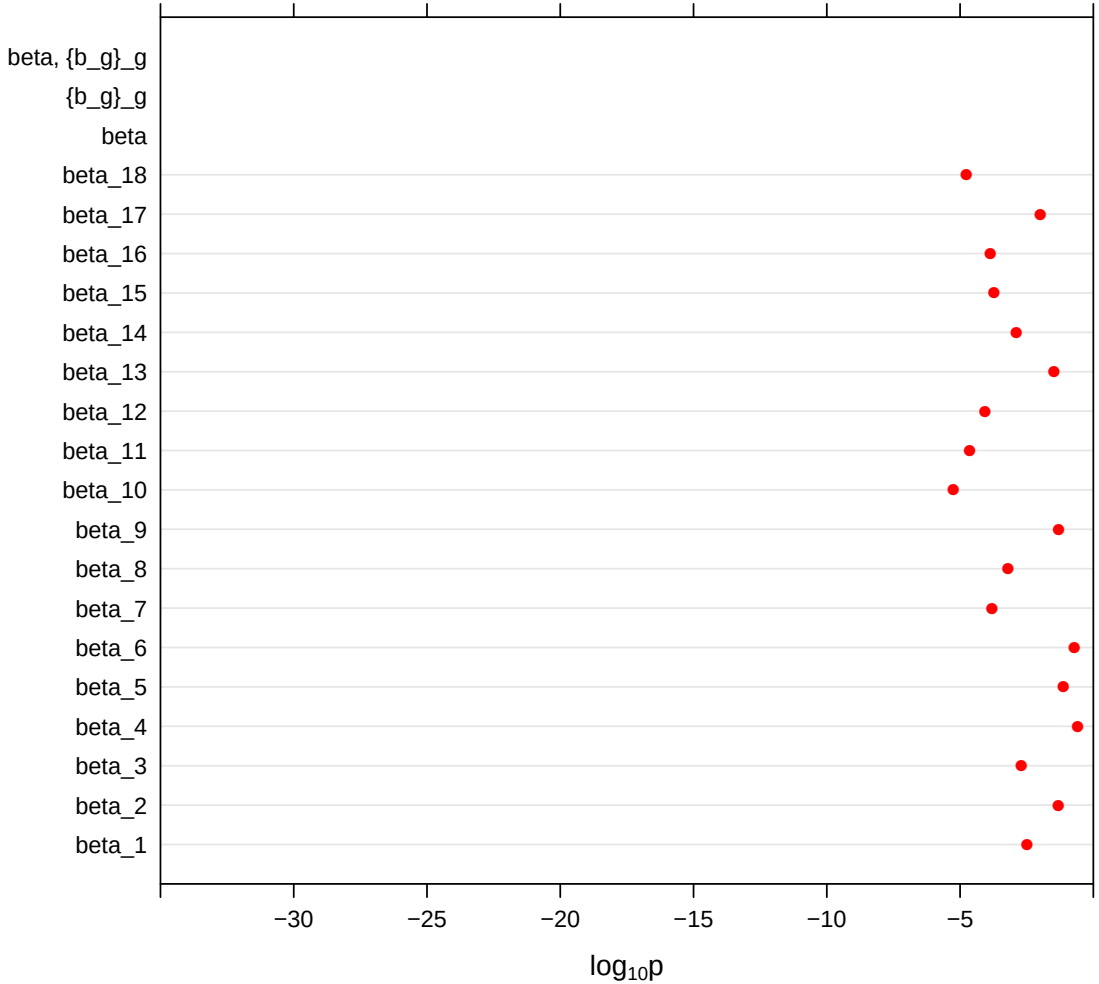
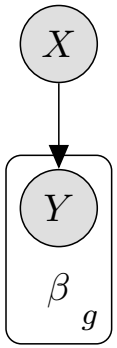
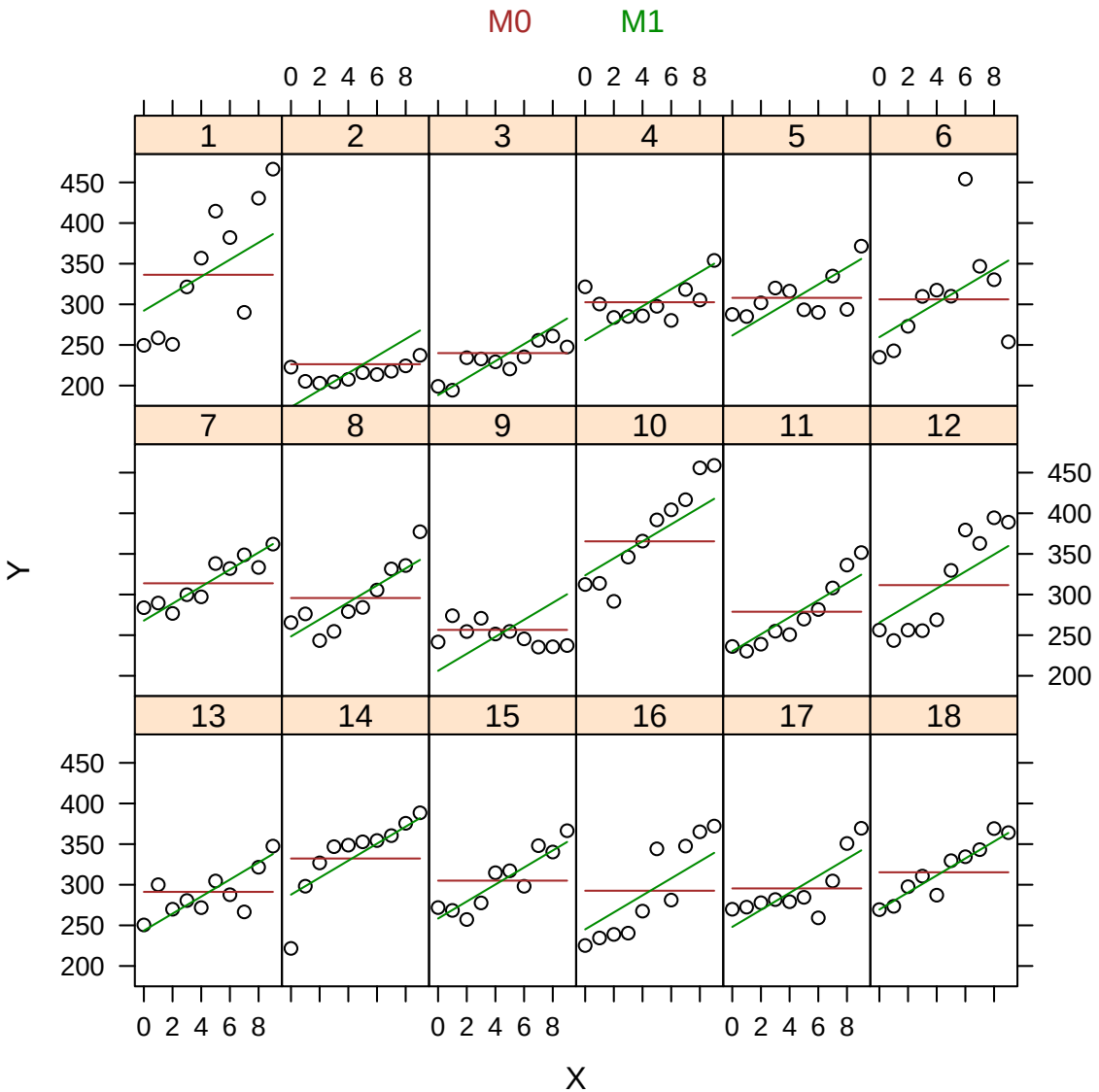
F1

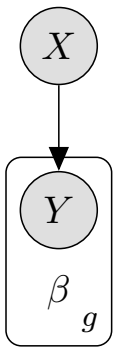

F1 vs F0: specific
beta, {b_g}_g
{b_g}_g
beta
beta_18
beta_17
beta_16
beta_15
beta_14
beta_13
beta_12
beta_11
beta_10
beta_9
beta_8
beta_7
beta_6
beta_5
beta_4
beta_3
beta_2
beta_1
−30
−25
−20
−15
−10
−5
log10p


X
Y
β
g



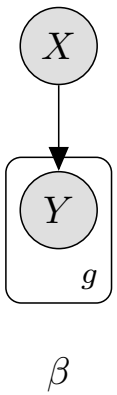
fixed

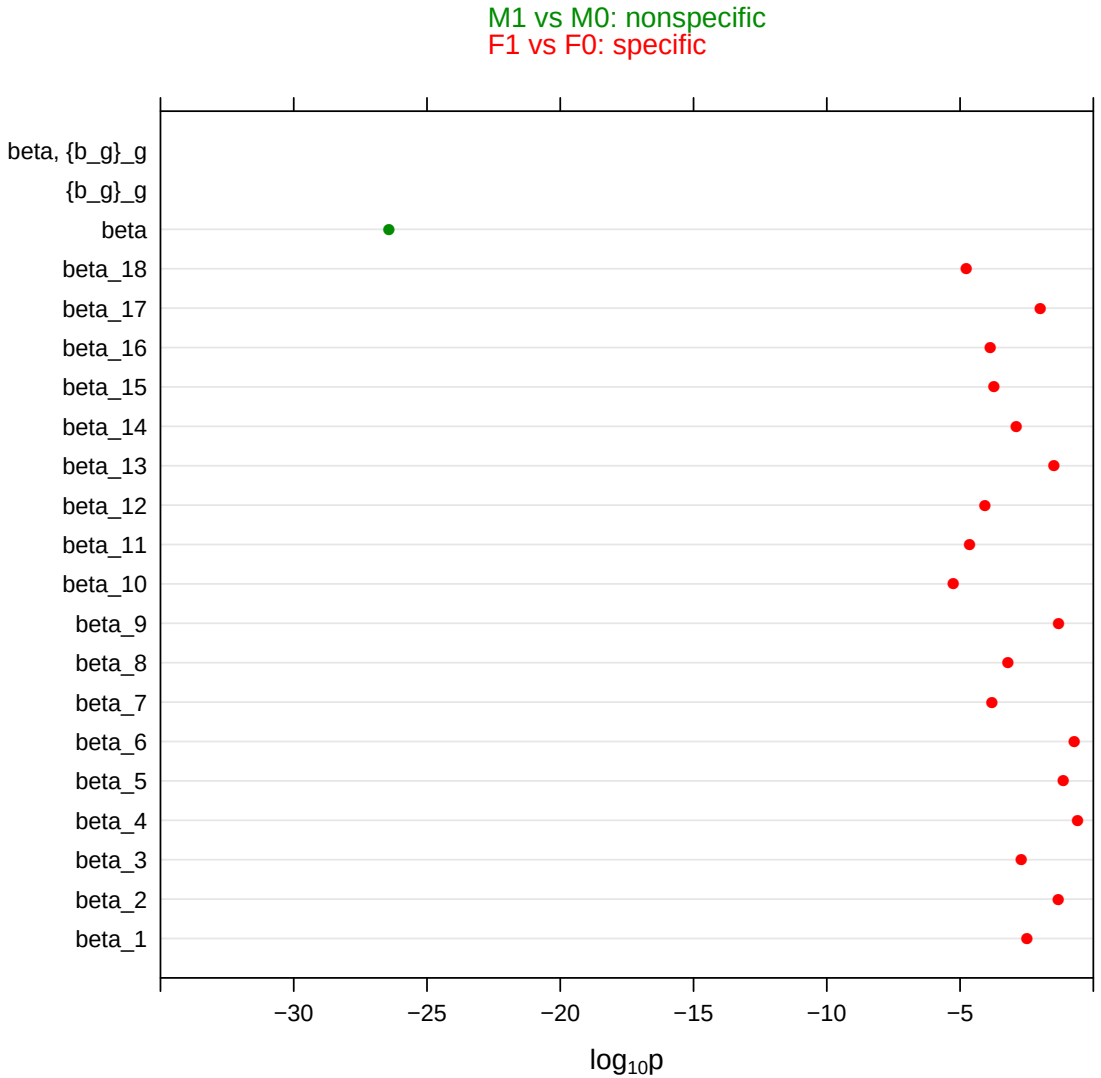
F1



mixed

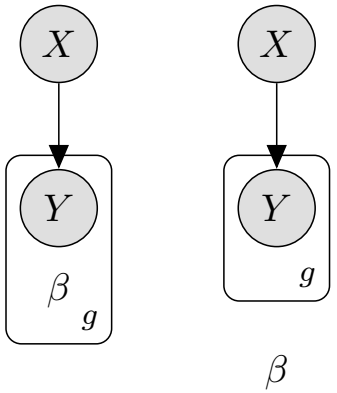
M1

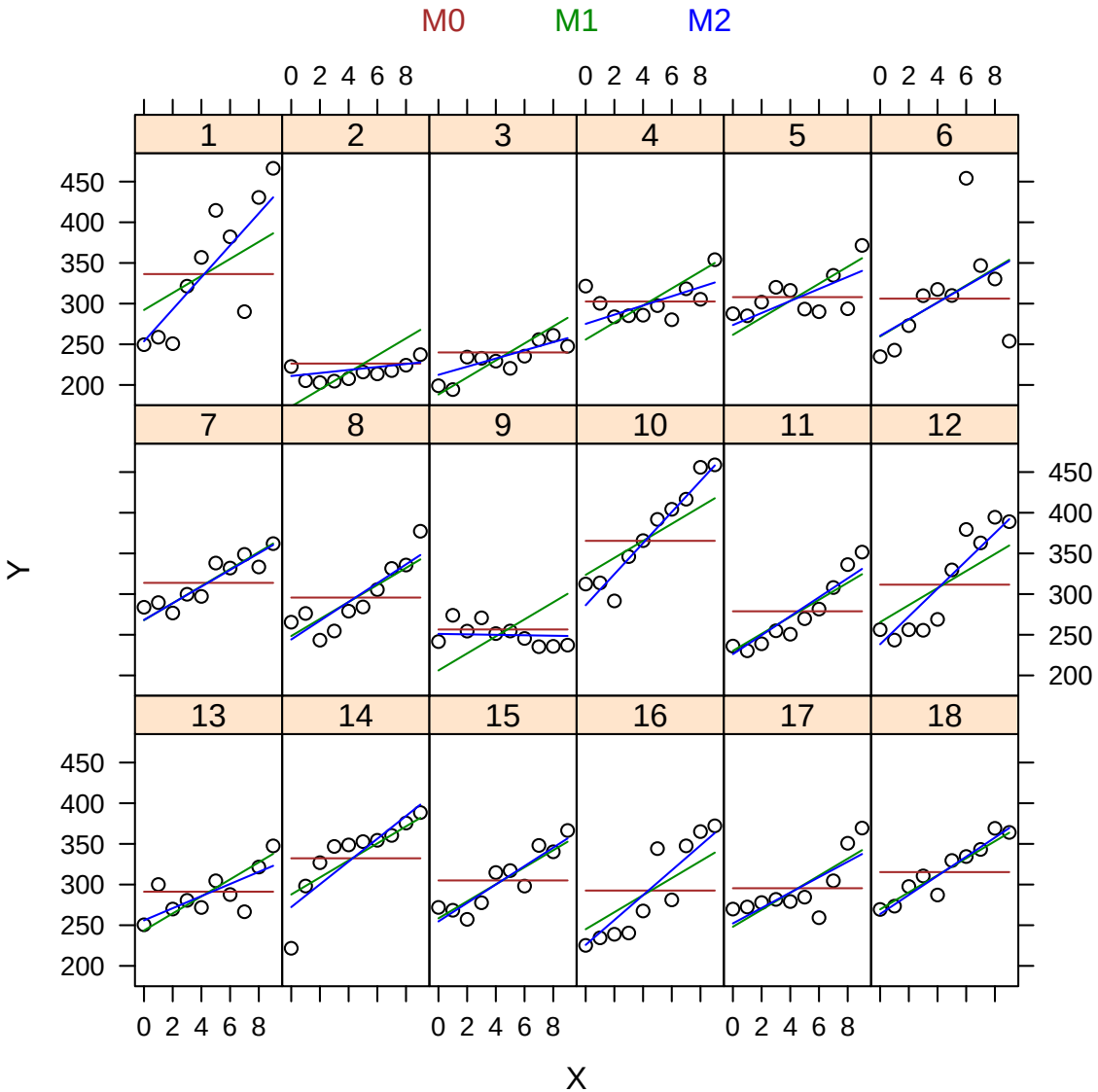




fixed mixed

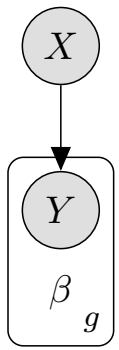
F1 M1





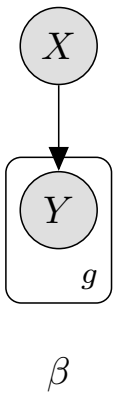
fixed

F1



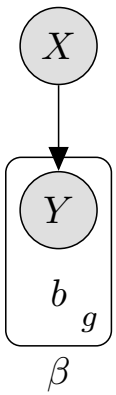
mixed

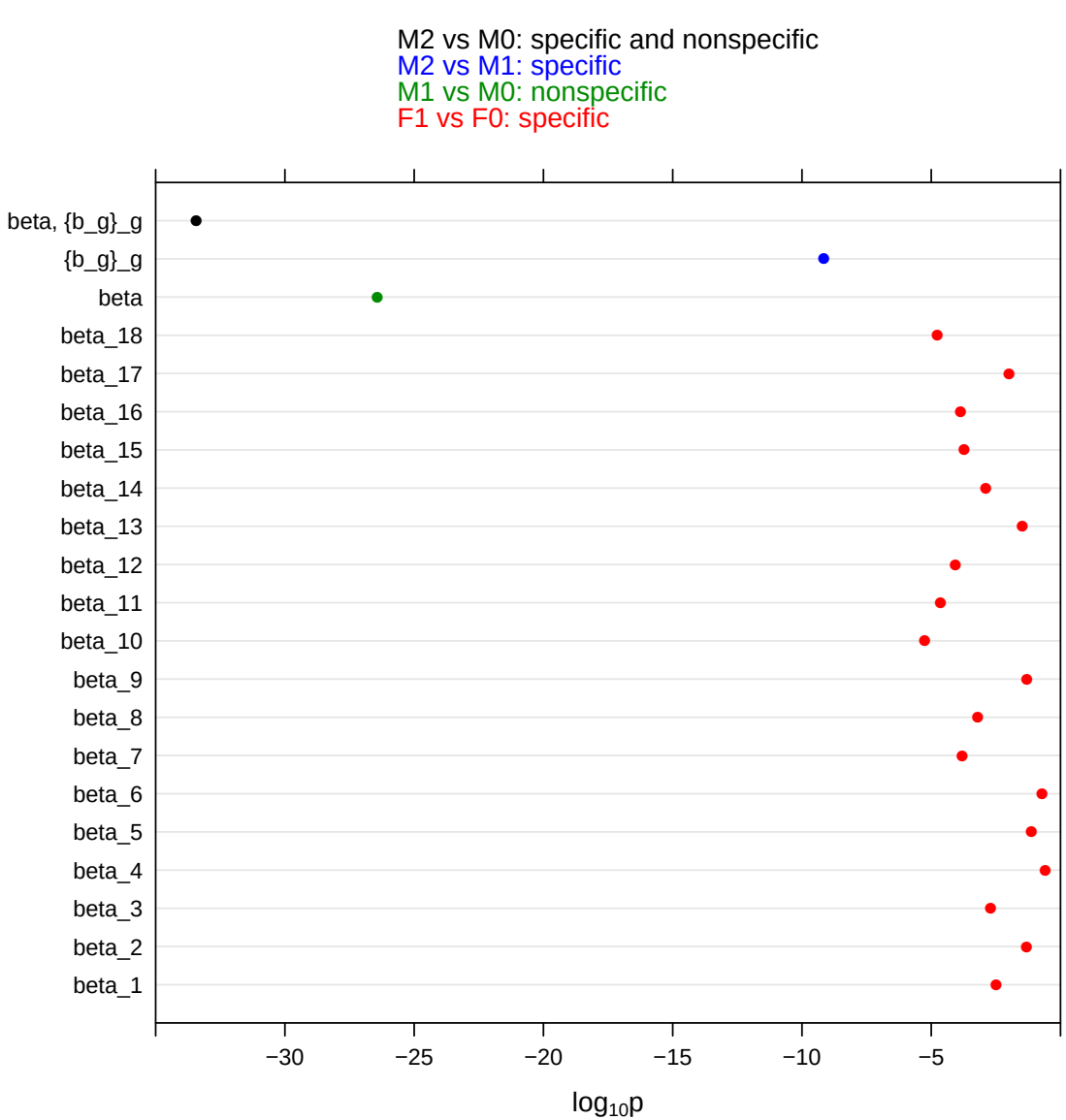
M1



mixed

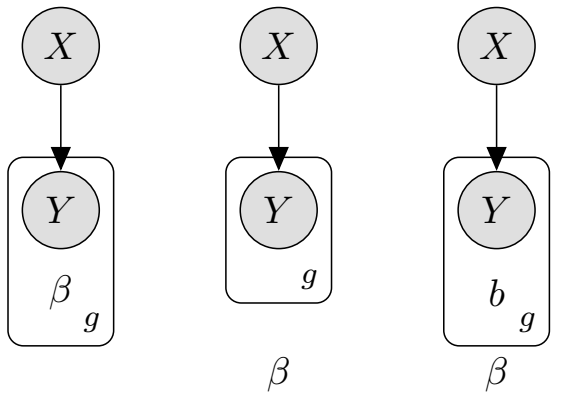
M2

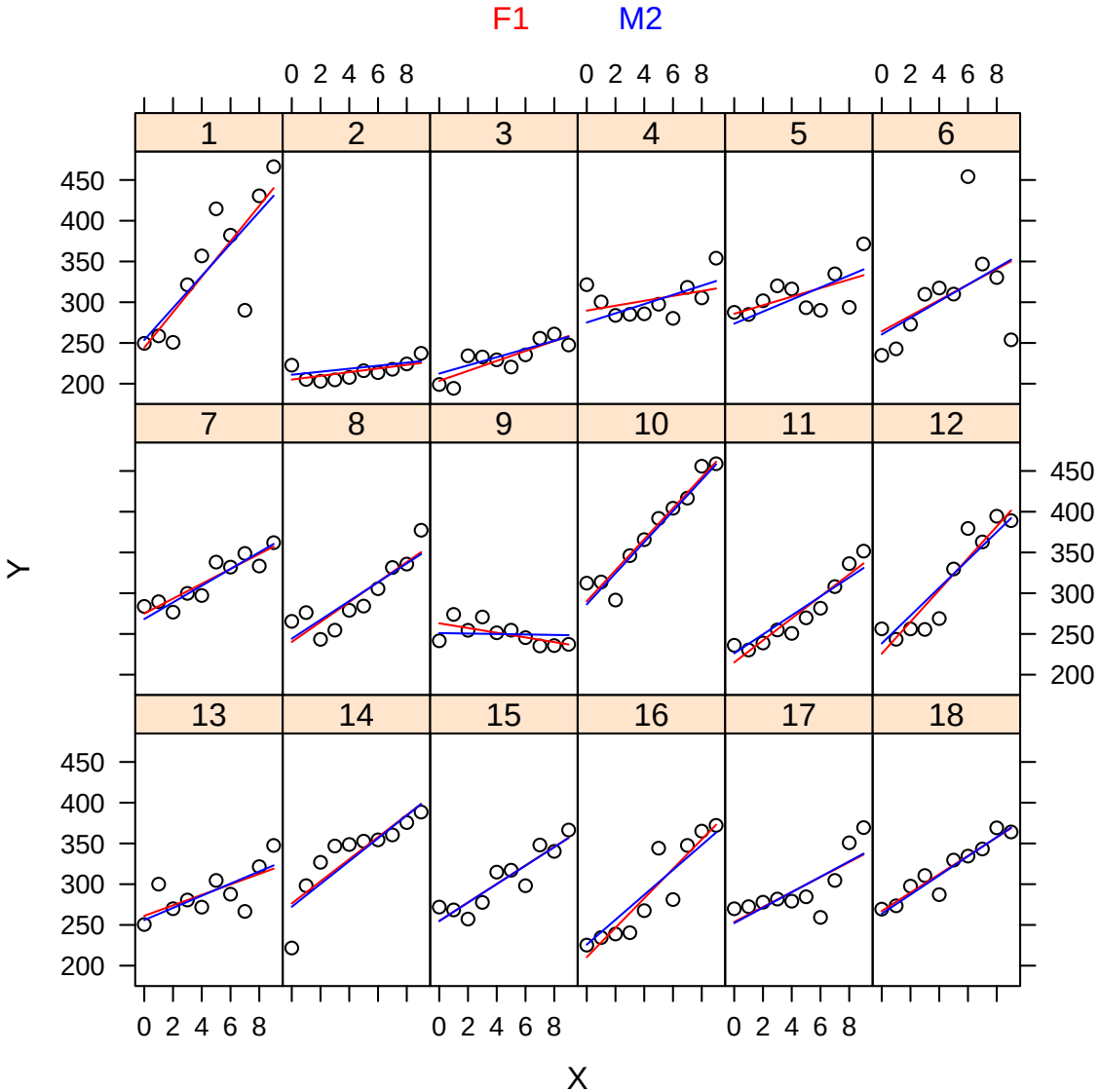




fixed mixed mixed

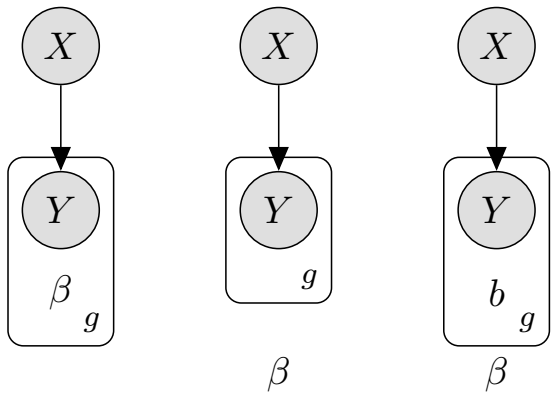
F1 M1 M2





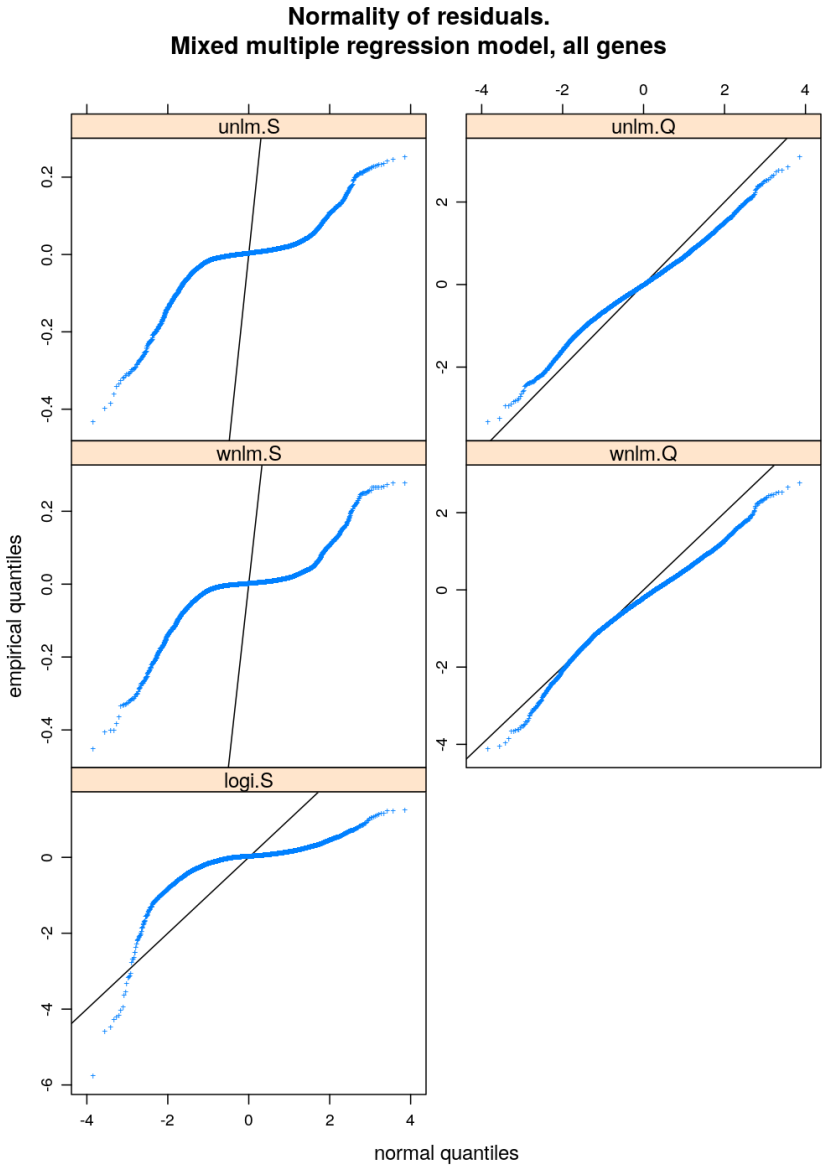
fixed mixed mixed

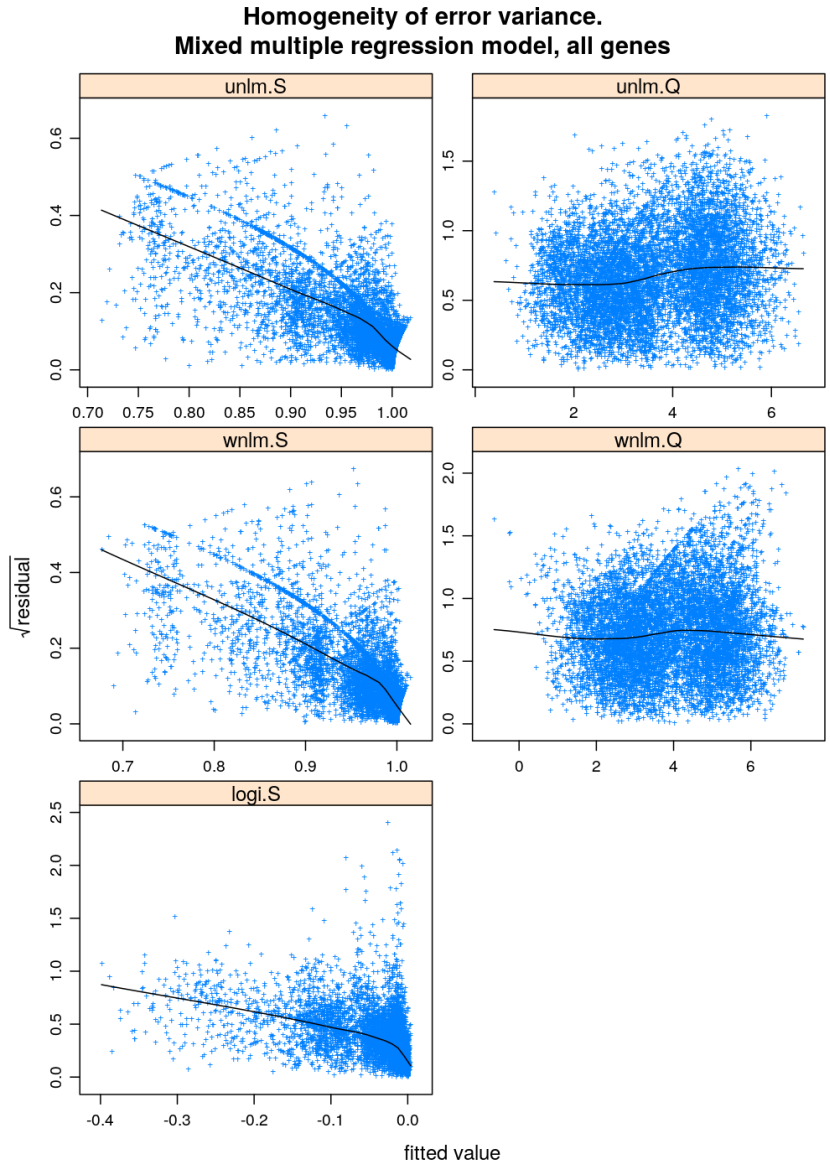
F1 M1 M2

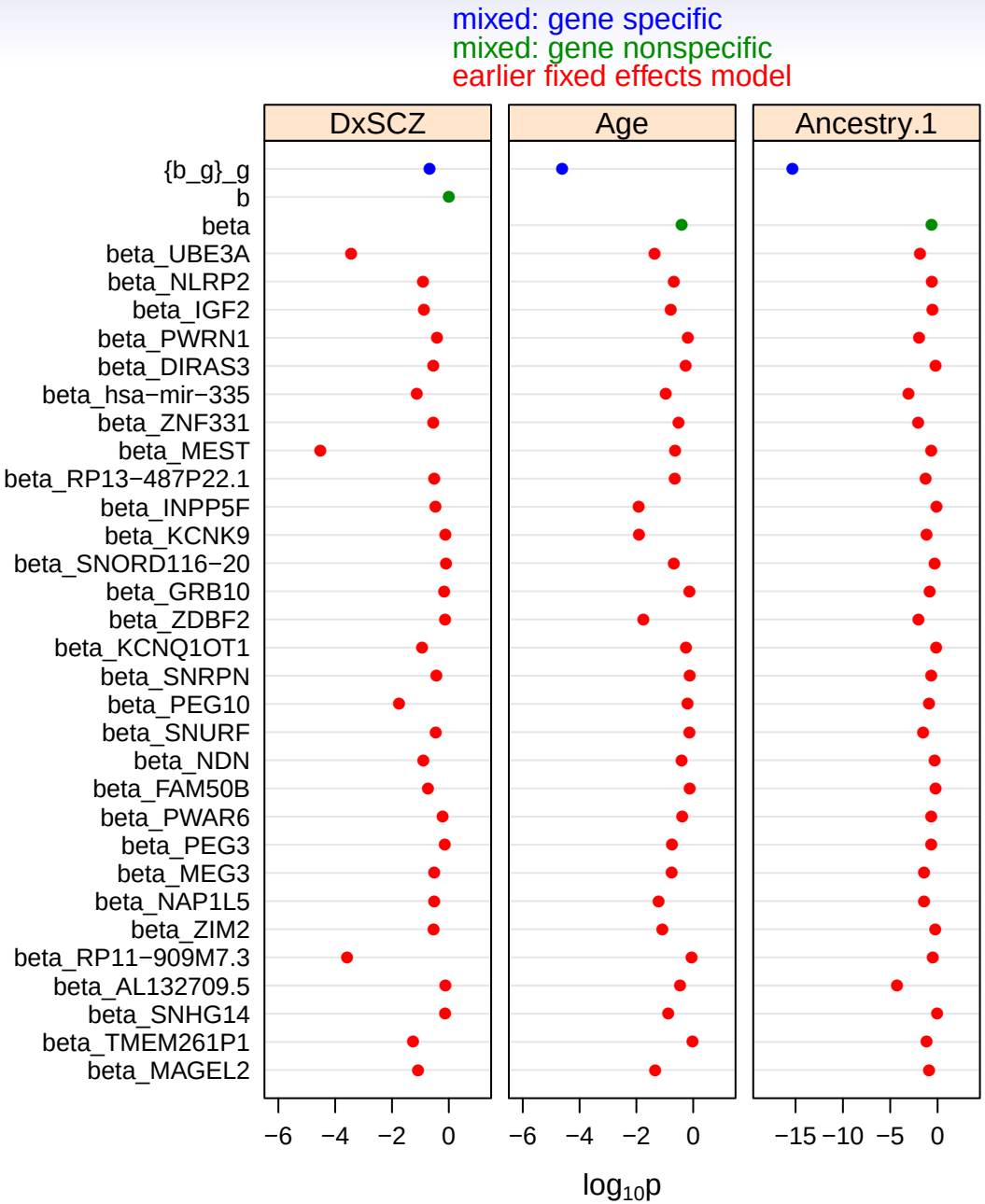


Mixed models and more:
https://attilagk.github.io/R-you-experienced/

Fitting mixed models on the CommonMind data






mixed: gene specific
mixed: gene nonspecific
earlier fixed effects model
DxSCZ
Age
Ancestry.1
{b_g}_g
b
beta
beta_UBE3A
beta_NLRP2
beta_IGF2
beta_PWRN1
beta_DIRAS3
beta_hsa−mir−335
beta_ZNF331
beta_MEST
beta_RP13−487P22.1
beta_INPP5F
beta_KCNK9
beta_SNORD116−20
beta_GRB10
beta_ZDBF2
beta_KCNQ1OT1
beta_SNRPN
beta_PEG10
beta_SNURF
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beta_NAP1L5
beta_ZIM2
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beta_AL132709.5
beta_SNHG14
beta_TMEM261P1
beta_MAGEL2
−6 −4 −2 0
−6 −4 −2 0
−15 −10 −5 0
log10p

Summary

- caution: model fit
- dependence of read count ratio on...

explanatory variable	gene nonspecific	gene specific
Schizophrenia (Dx)	-	-
Age	-	+
Ancestry.1,3	-	+
Gender	-	+

- interpretation
  1. no detectable link between imprinting and schizophrenia
  2. age, genetics and gender affect imprinting; genes vary

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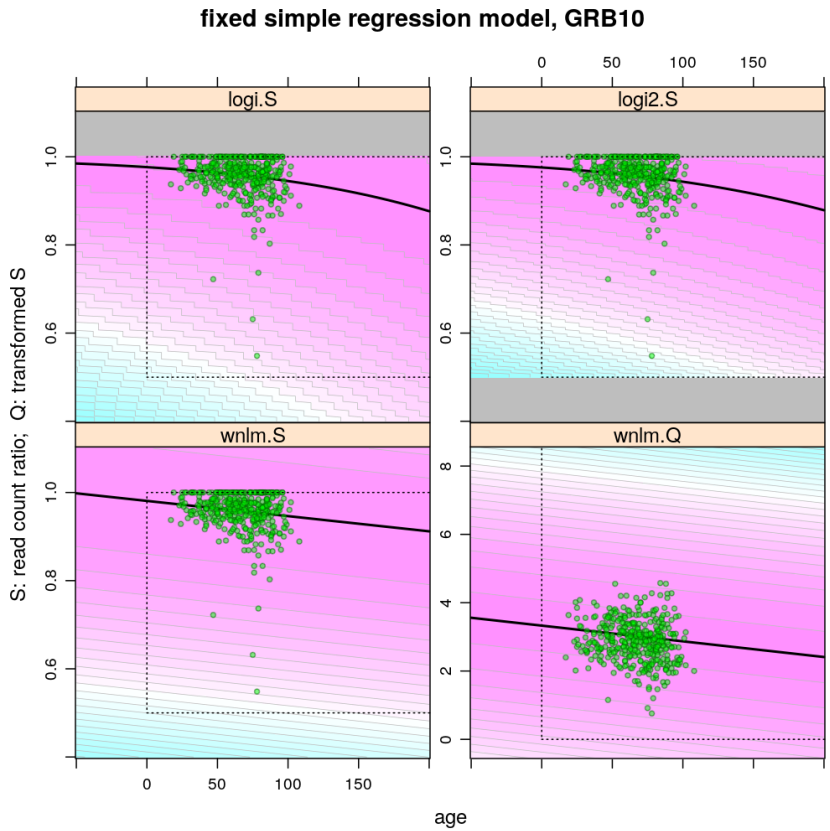
End

- manuscript submitted
  Attila Gulyás-Kovács, Ifat Keydar, Eva Xia, Menachem Fromer, Gabriel Hoffman, Douglas Ruderfer, CommonMind Consortium, Ravi Sachidanandam, Andrew Chess
- special thanks
  Chaggai Rosenbluh
- mixed models and more
  https://attilagk.github.io/R-you-experienced/