Genomic Imprinting in the Human Brain

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Introduction: the allelic bias of imprinted genes

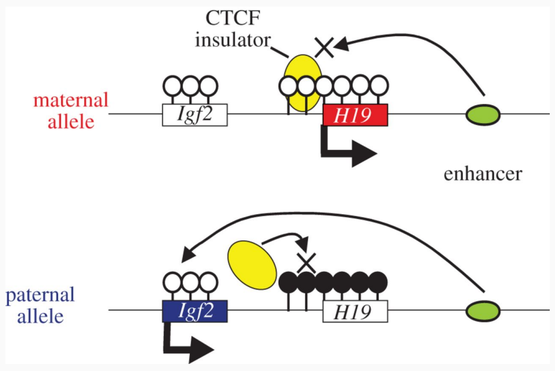


Fig. 1: Renfree et al 2012 Philos Trans R Soc Lond B

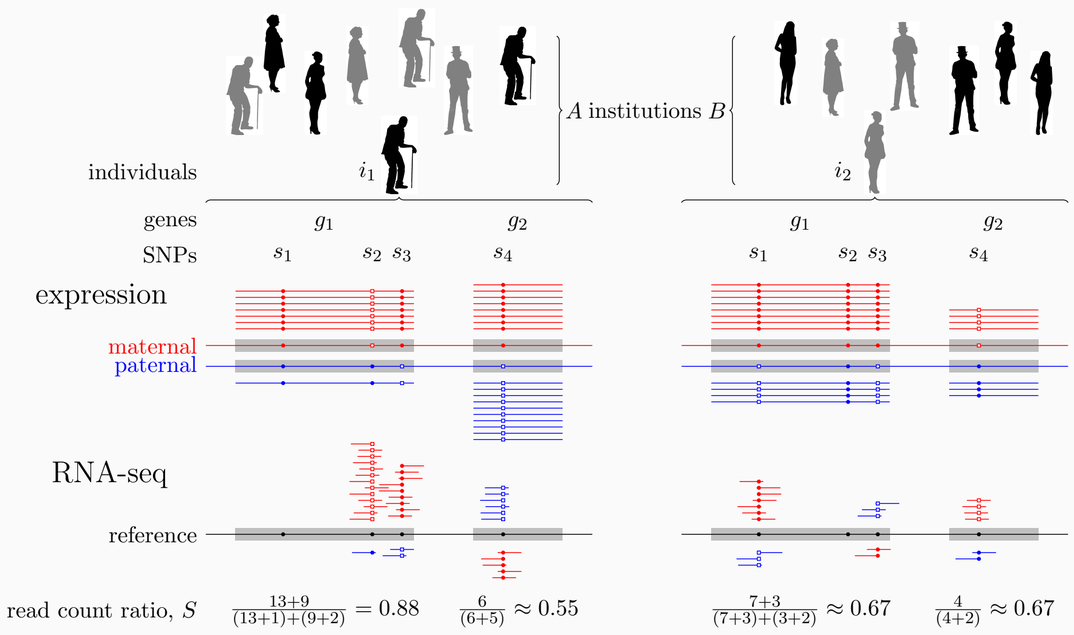
Imprinting is thought to concern some 100 or more genes expressed in various tissues and ages, notably much of the embryo, the placenta, and the adult brain. Comprehensive mapping between imprinted genes, tissues and ages has just begun. Although the neuro-psychiatric function of imprinted genes is unclear, they likely play some role in psychotic spectrum conditions.

Imprinted genes express their maternal and paternal allele asymmetrically; we call this *allelic bias*. Our study infers allelic bias from RNA-seq *read count ratio* based on the CommonMind Consortium's data.

We aim at...

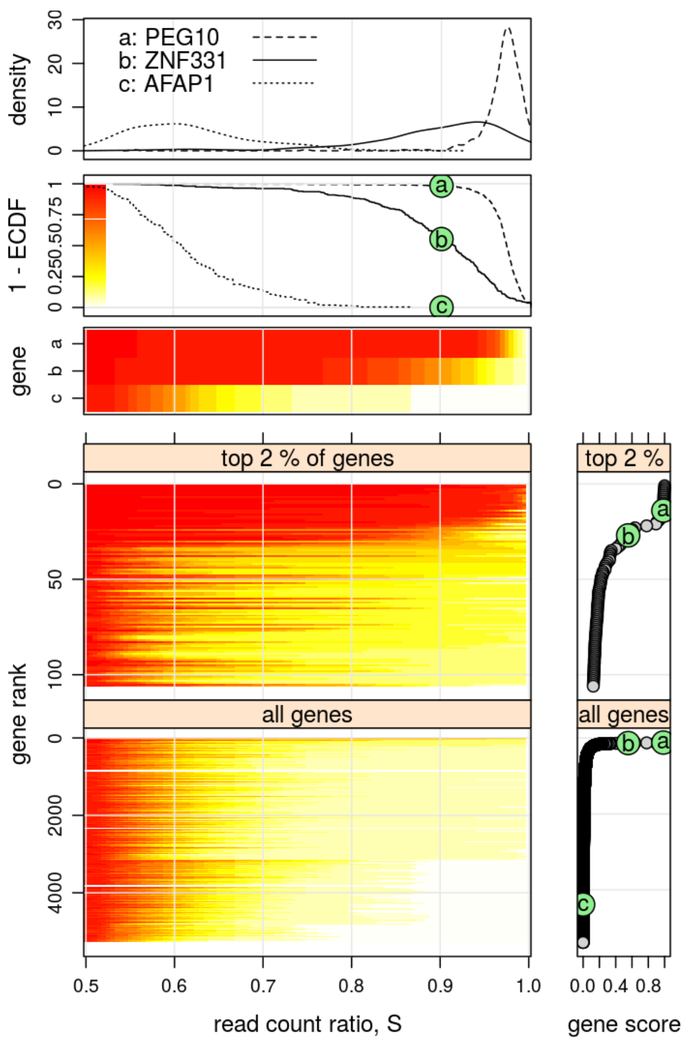
1. the number and identity of imprinted genes in the human dorsolateral prefrontal cortex
2. the identification of predictors of allelic bias among age, ancestry, diagnosis of schizophrenia or affective spectrum disorder, etc.

RNA-seq read count ratio reports on allelic bias



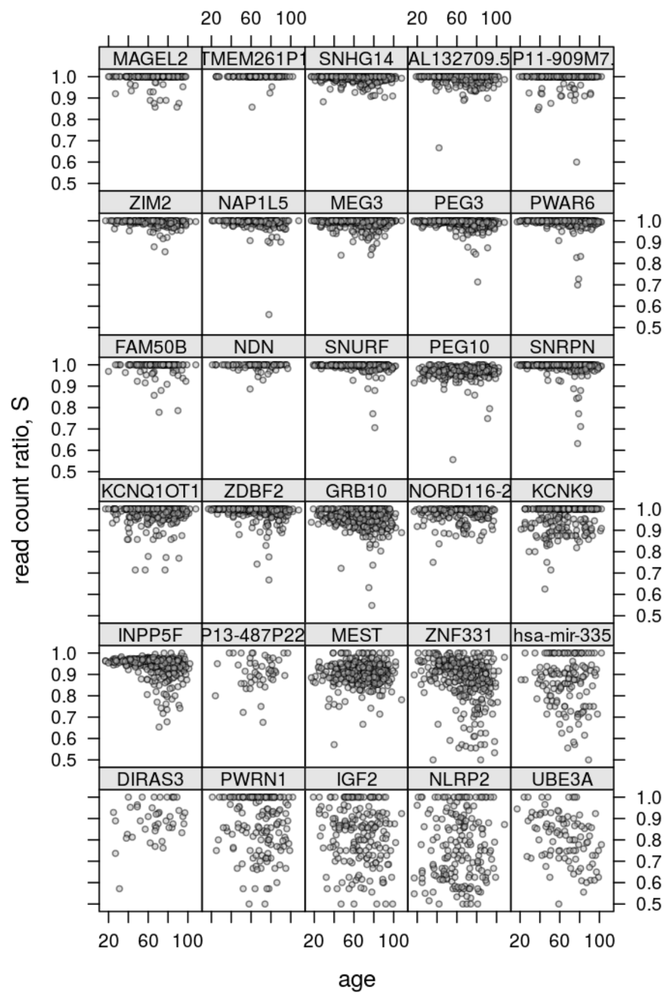
Allelic bias across individuals and genes

across all genes



The figure shows, for each gene, a large inter-individual variation of read count ratio, which originates partly from variation of allelic bias and partly from technical noise. We scored and ranked genes based on their inter-individual distribution function ECDF and inferred genes with the highest ranks—among other criteria—to be imprinted.

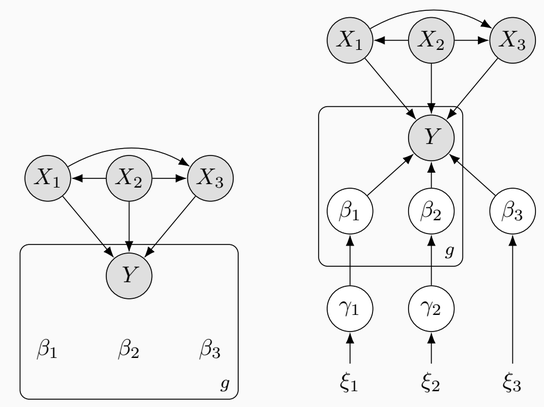
across imprinted genes



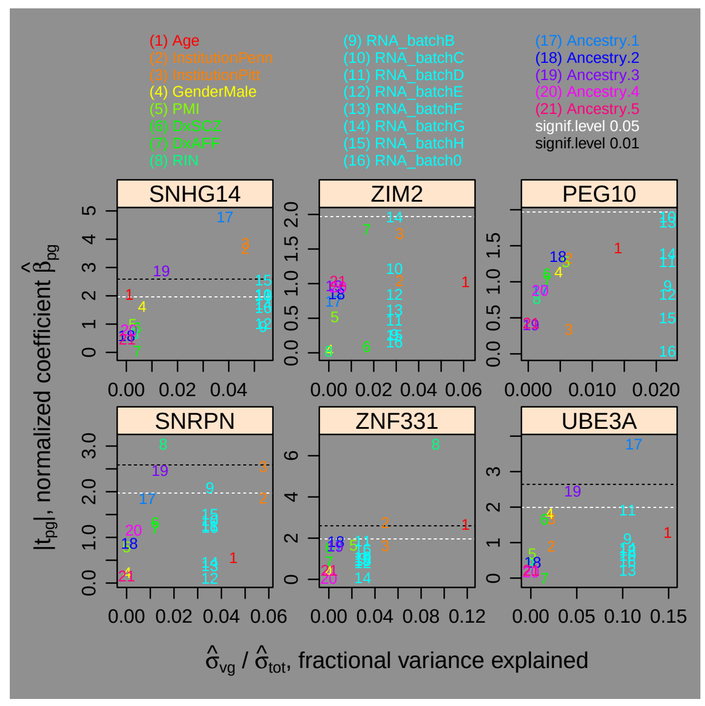
Shown are joint distributions of read count ratio and age for the 30 genes we called imprinted, ordered according to gene score. These distributions appear to suggest that allelic bias decreases (e.g. ZNF331) or increases (e.g. KCNK9) with age or is independent of age (e.g. MEST). However, the interdependence of age and other predictors calls for model-based inference.

Predictors of allelic bias

Illustration of the *fixed effects (left)* and the *mixed (right)* regression model. Using these models we inferred the subset of predictor $\{X_i\}$ on which the read count ratio Y significantly depends.



fixed effects model: weak significance



mixed model: age & ancestry effect

term	ΔAIC	p-value
Age	1.8	6.5e-01
Age.Gene	**-23.4**	**2.5e-06**
Ances1	-0.2	1.3e-01
Ances1.Gene	**-56.8**	**4.8e-13**
Gender.fix	1.0	3.2e-01
Gender.ran	2.0	1.0
Gender.Gene	**-5.8**	**5.2e-03**
Dx.fix	3.9	9.5e-01
Dx.ran	2.0	1.0
Dx.Gene	0.5	2.1e-01

Summary & conclusions

- at most 100 imprinted genes in the brain, several previously not described
- technical noise substantially masks biological predictors of allelic bias
- powerful mixed models suggest allelic bias depends on ancestry and age, but not schizophrenia; these dependencies, however, vary across genes

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