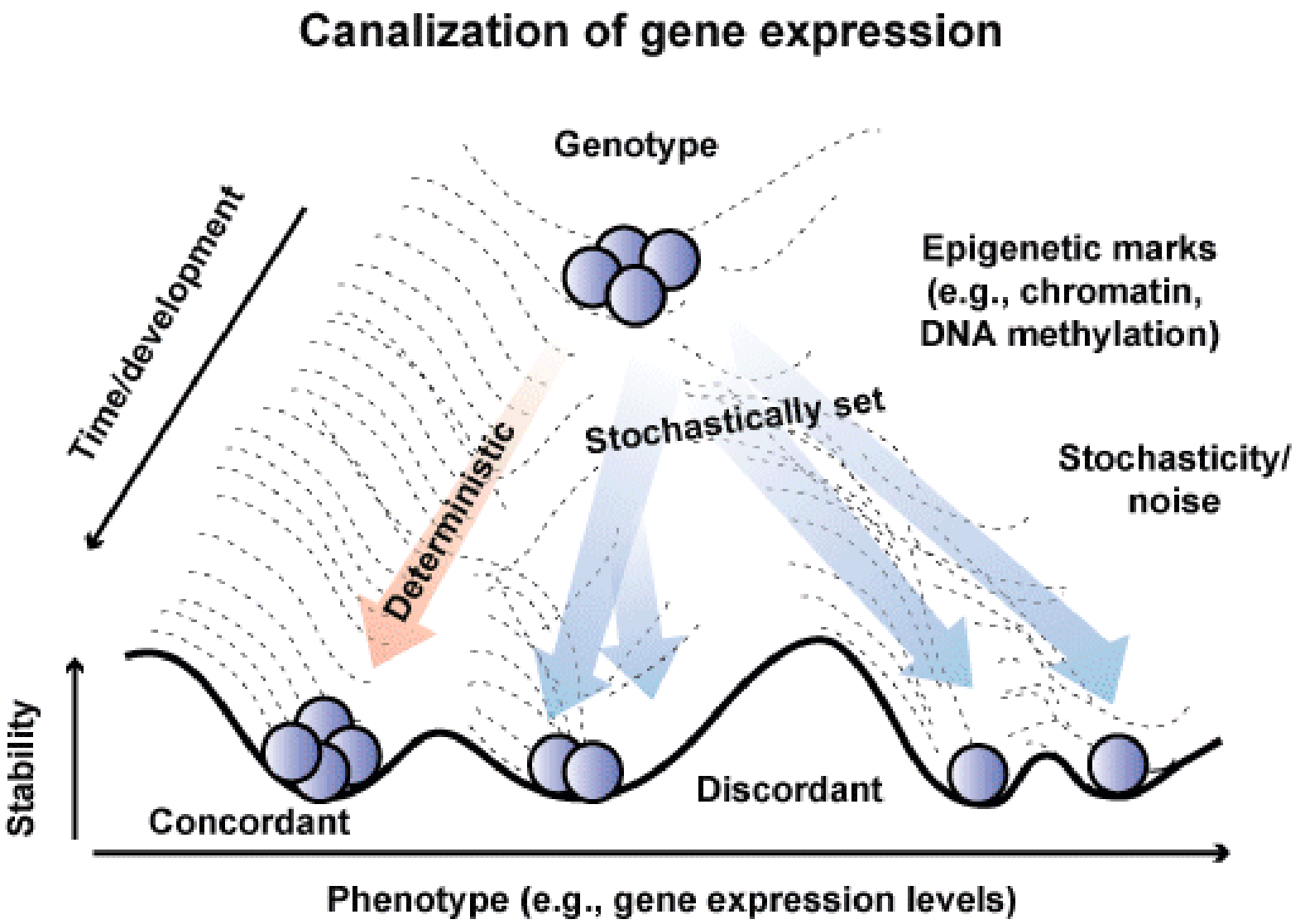
The transcriptional legacy of developmental stochasticity

Jesse Gillis

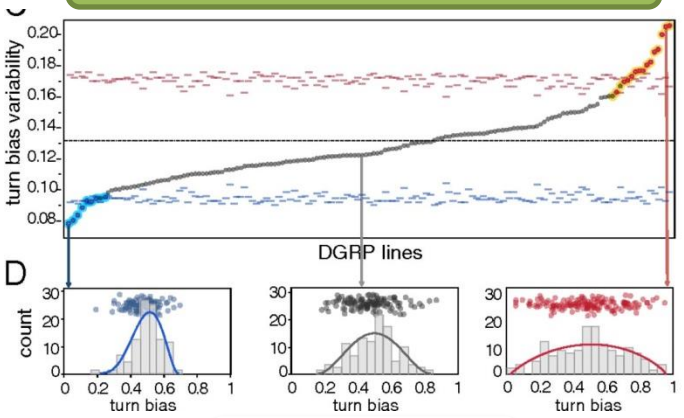


Waddington landscape

Identical genomes yield different phenotypes

Twins have different fingerprints

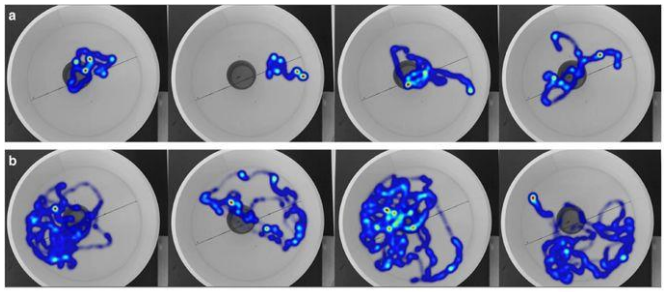
Behavioral differences



Aryoles et al (2015)

Clonal cats have different patterning

Raser and O'Shea (2005)



Bierbach et al (2017)

A delicate balance

Developmental specification

- Allows for genetic buffering and promotes robustness

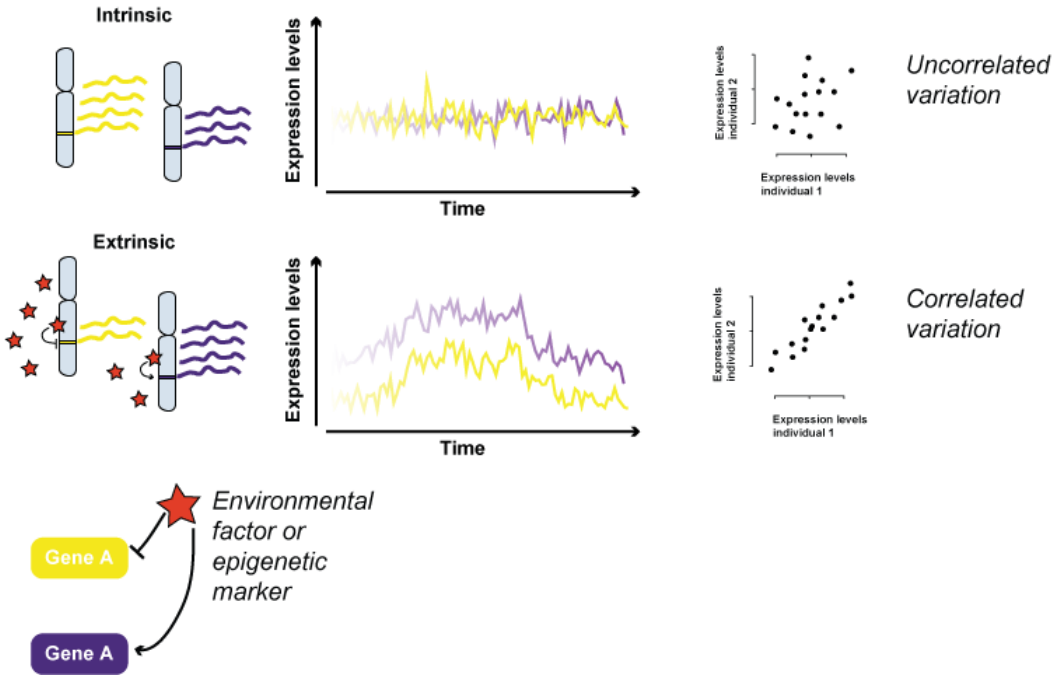
Developmental variation

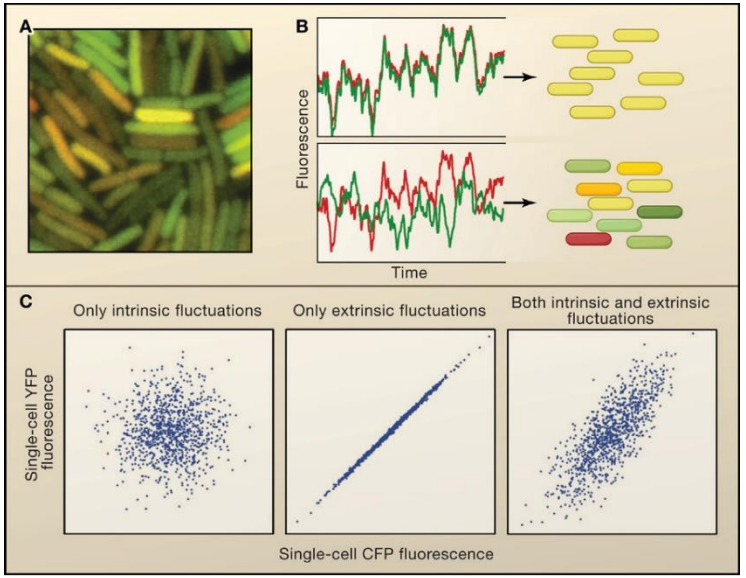
- Increases adaptability and evolvability

Outcome is individuality

If gene expression reflects epigenetic states, are there markers of identity that remain over time?

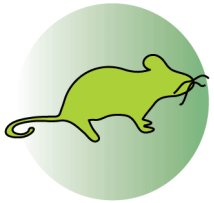
Intrinsic versus extrinsic noise





Raj and van Oudenaarden, 2008

Genetic background has a large impact

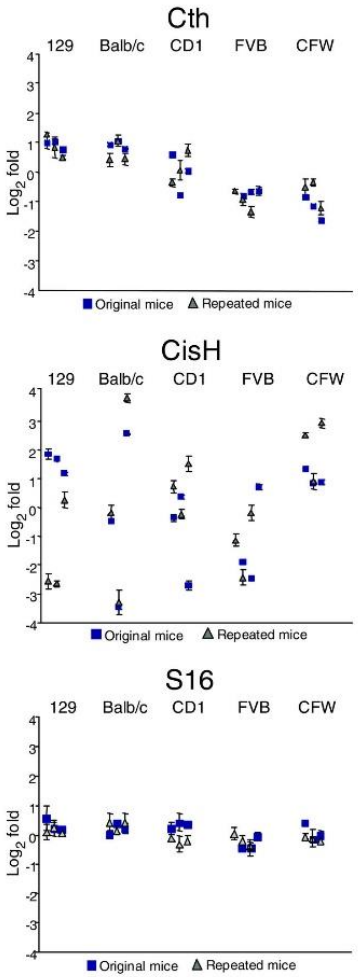


…the average rate of successful translation from animal models to clinical cancer trials is ***less than 8%.***

Mak et al. 2014

The evidence that most ***gene regulation is trans and strongly influenced by genetic background****, suggests that pathways that are modified by an allelic variant, may only exhibit differential expression in the specific genetic backgrounds in which they were identified.*

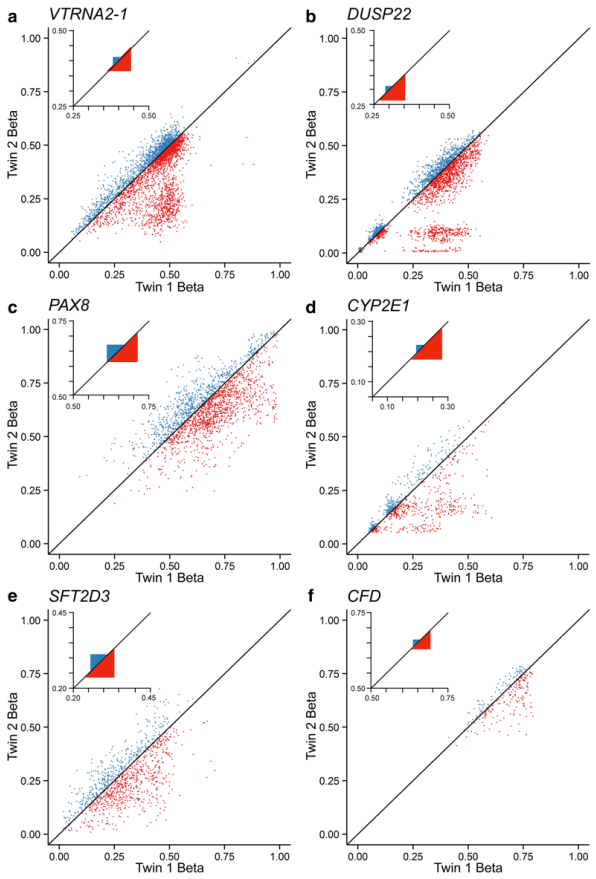
Noyes et al. 2010



Pritchard et al. 2006

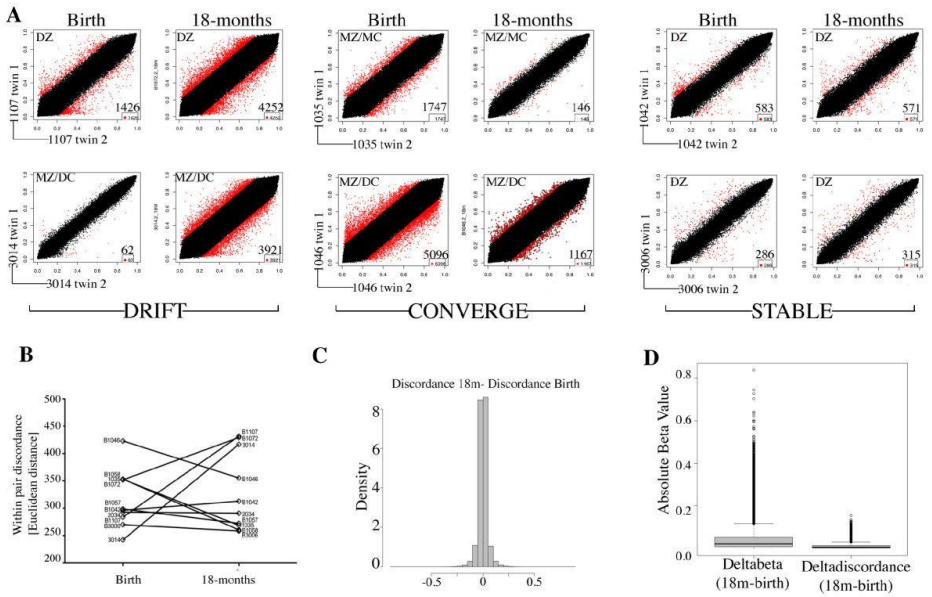
Human data is highly variable

Higher methylation similarity among MZ over DZ



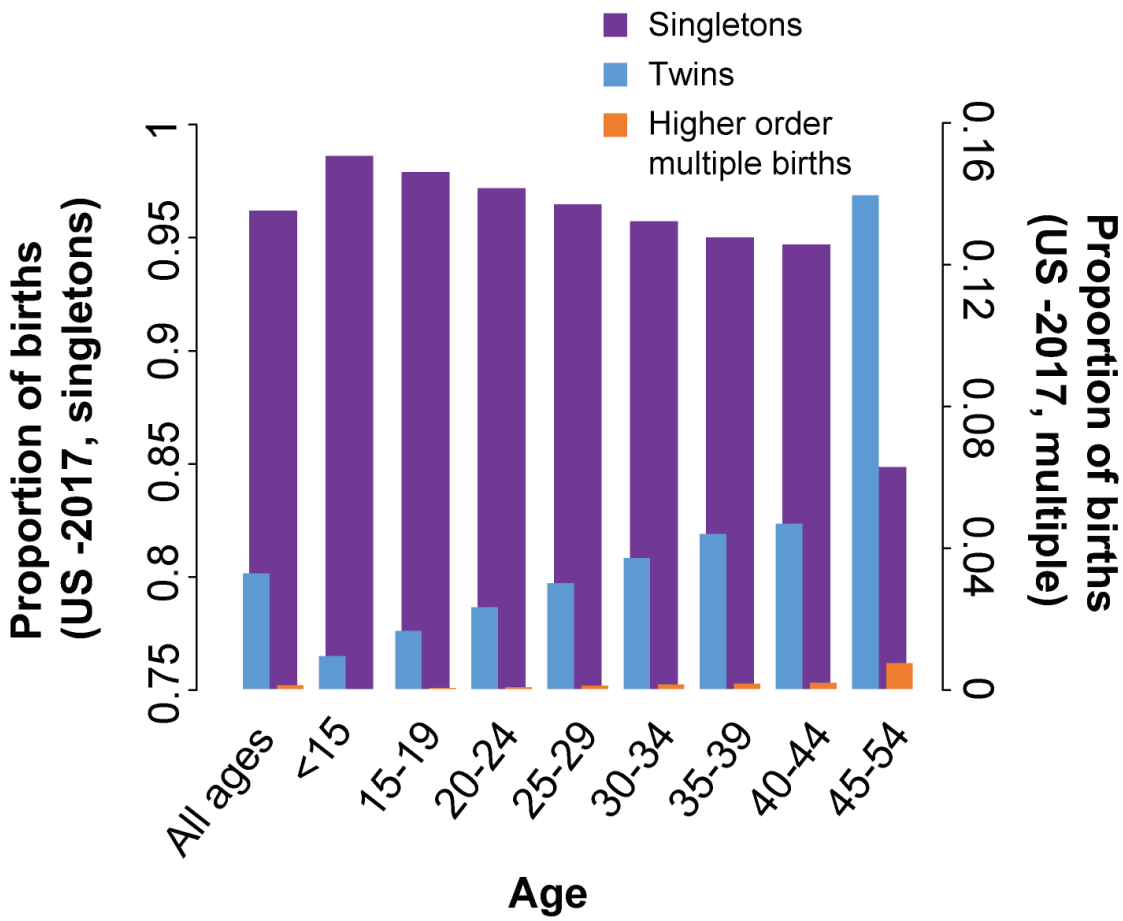
Van Baak, Coarfa et al (2018)

Methylation differences across time may be twin specific



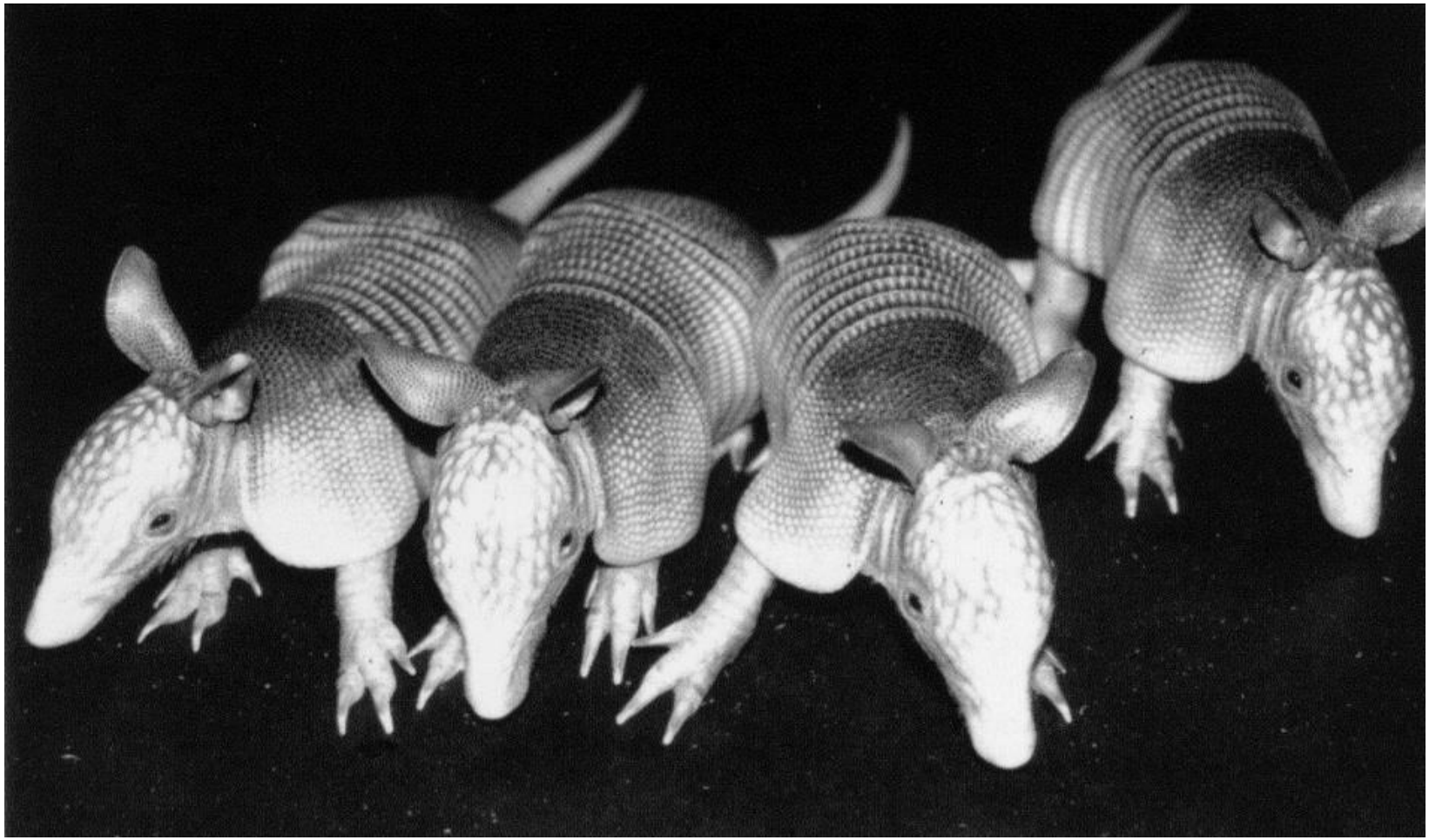
Martino et al (2013)

Human twins are unusual



Dasypus novemcinctus

Monozygotic quadruplets



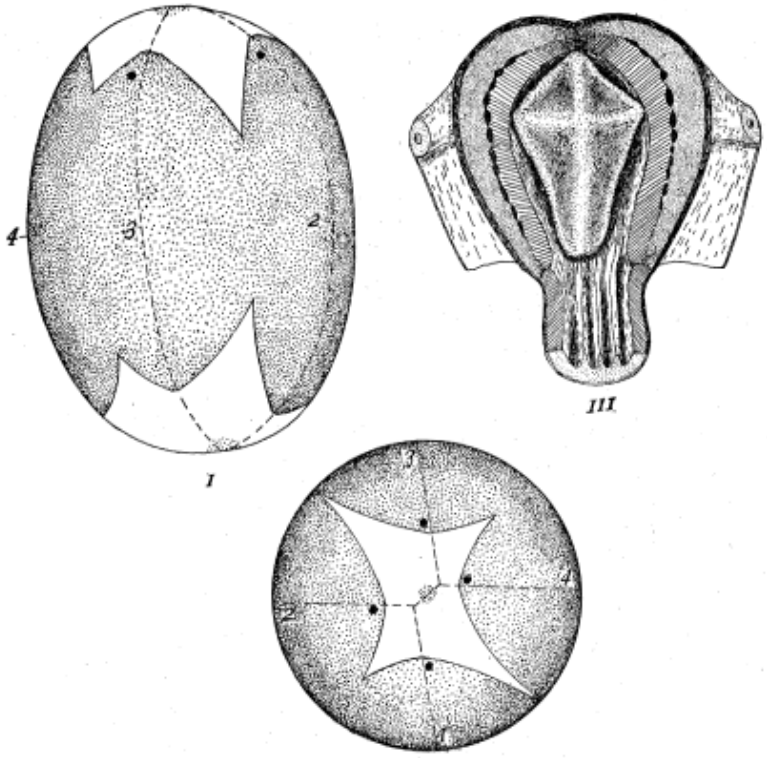


FIG. 1. A diagrammatic representation of an approximately dorsal view of a chorionic vesicle taken from the uterus about two weeks (estimated) before the young would have been born. Three of the ovoid areas are in view, and the broken lines represent the lines along which the amniotic partitions meet the inside wall of the chorion. The clear areas at the ends are broken into by the scallops of the ovoid areas. In this, as in the succeeding figure, the points of attachment of the umbilical cords are indicated by large dots. Note especially that the indentations between the scallops of areas 3 and 4 are much shallower than those between areas 2 and 3, leaving a broader connection between the former than between the latter. This is an indication that embryos 3 and 4, located respectively on dorsal and left lateral areas (similarly embryos 1 and 2, located on the ventral and right lateral areas), are natural pairs. For the significance of this arrangement see table and text. One half natural size.

FIG. 2. A view of the distal end of the preceding figure. This is introduced to show the relation existing between the amniotic partitions within the chorionic cavity. The figure also brings out the fact that the embryos may be paired, together with the ovoid areas to which they are attached by the umbilical cords. One half natural size.

FIG. 3. This shows a chorionic vesicle *in situ*, as revealed by splitting open the uterus along the mid-ventral line. The age of this vesicle is estimated at one month. Unfortunately the splitting was done before the specimen reached our hands, and extended so deep as to divide the vesicle into two parts. The parts, however, were well preserved *in situ*, and the reconstruction could be made with certainty. Note that the vesicle is octaedronal in shape, and that its entire surface is covered with villi. Natural size.

Vol. XVII. *August, 1909.* *No. 3.*

BIOLOGICAL BULLETIN

A CASE OF NORMAL IDENTICAL QUADRUPLETS IN THE NINE-BANDED ARMADILLO, AND ITS BEARING ON THE PROBLEMS OF IDENTICAL TWINS AND OF SEX DETERMINATION.[1]

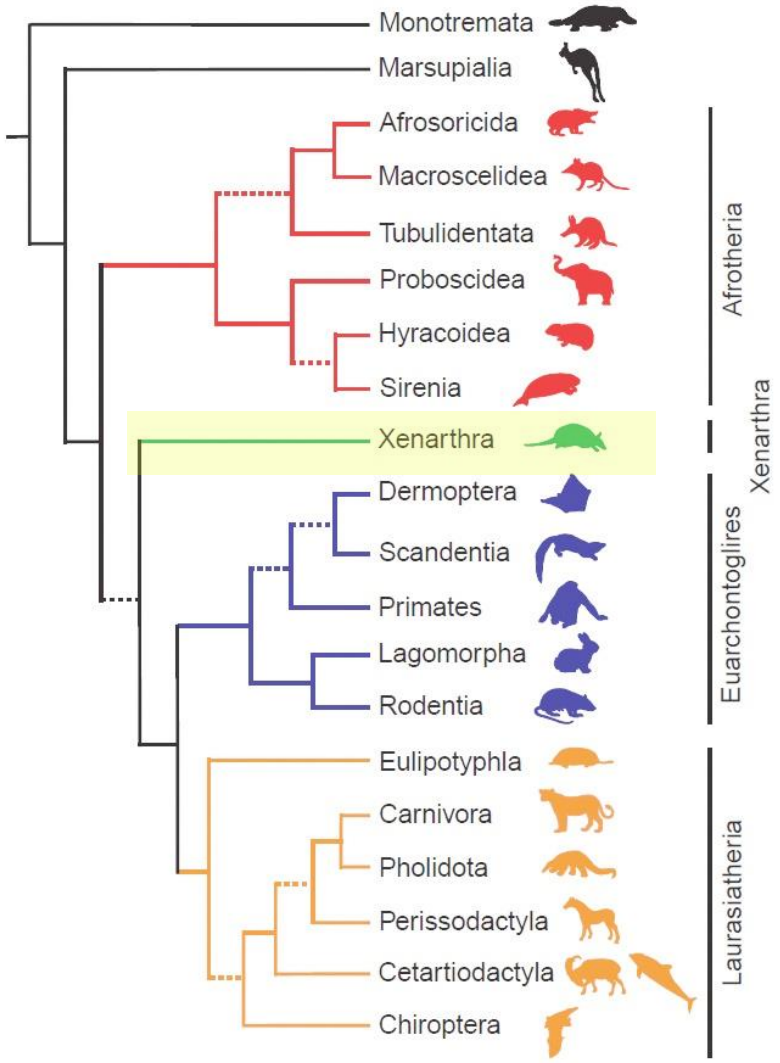
H. H. NEWMAN AND J. THOS. PATTERSON.

Set A (Females).		Set B (Males).	
No. 1	556 (+ 1) plates[1]	No. 1	571 (+ 2) plates
No. 2	555 (+ 2) "	No. 2	573 (+ 1) "
No. 3	553 (+ 2) "	No. 3	569 "
No. 4	551 (+ 4) "	No. 4	568 "

[1] The numbers enclosed in parentheses refer to certain rudimentary plates that are more or less united with other plates. It is impossible to tell in the embryos whether

After all, the development of the fœtal membranes is a matter of secondary interest, as compared with the more fundamental problem of the identity of the embryos of a set, and its corollary that of sex determination. The bearing of this work on the latter problem is obvious, and we hope that a study of the early developmental stages will lend a solution to this problem, and also furnish a satisfactory explanation of the puzzling question of "identical twins"; and thus raise this explanation from the plane of conjecture to the dignity of observed fact.

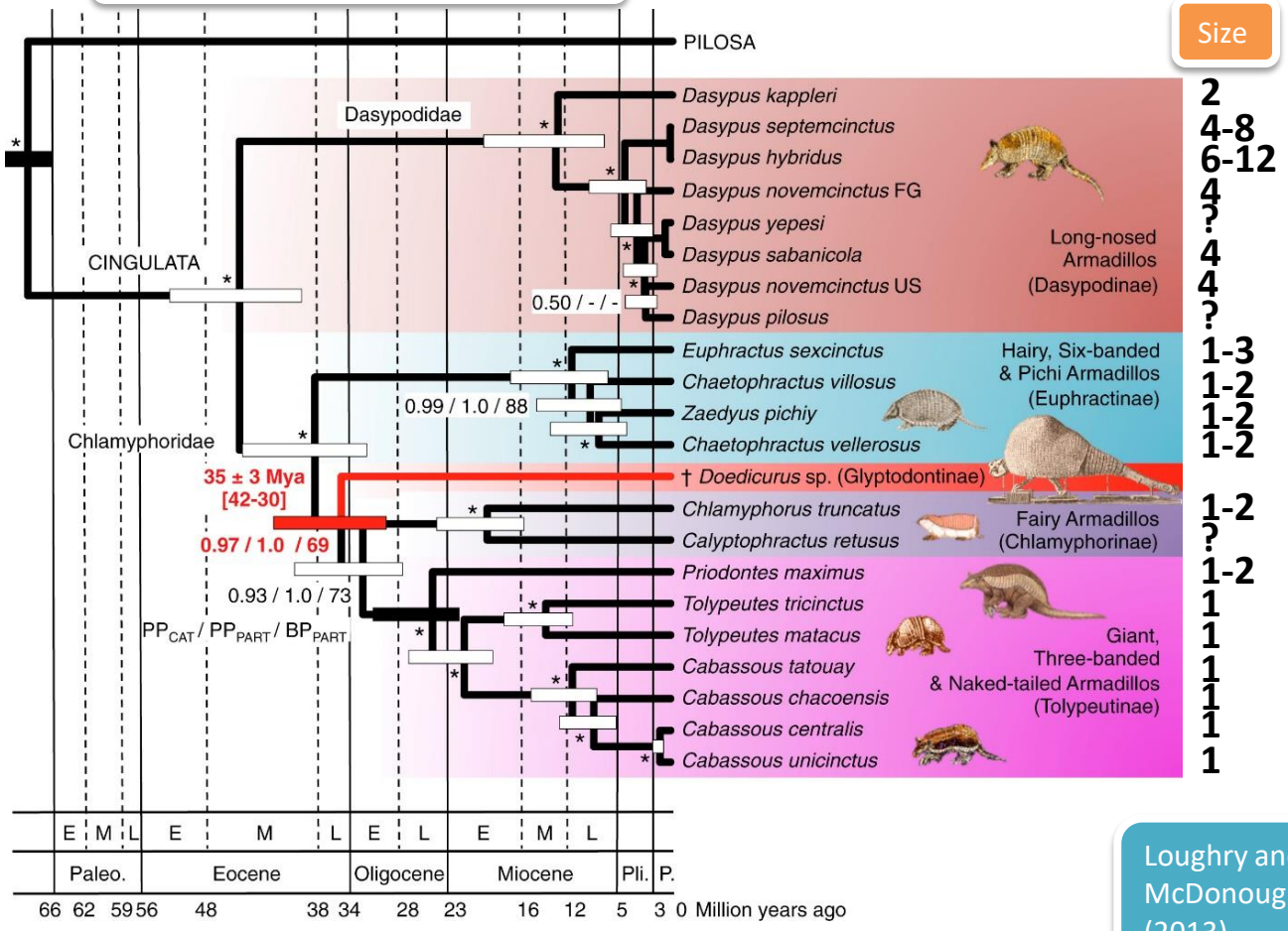
AUSTIN, TEXAS,
April 30, 1909.



New World Mammal

Litter sizes across the armadillo species

Phylogeny and molecular timescale



Delsuc et al (2016)

Size

2
4-8
6-12
4
?
4
4
?
1-3
1-2
1-2
1-2
1-2
?
1-2
1
1
1
1
1
1

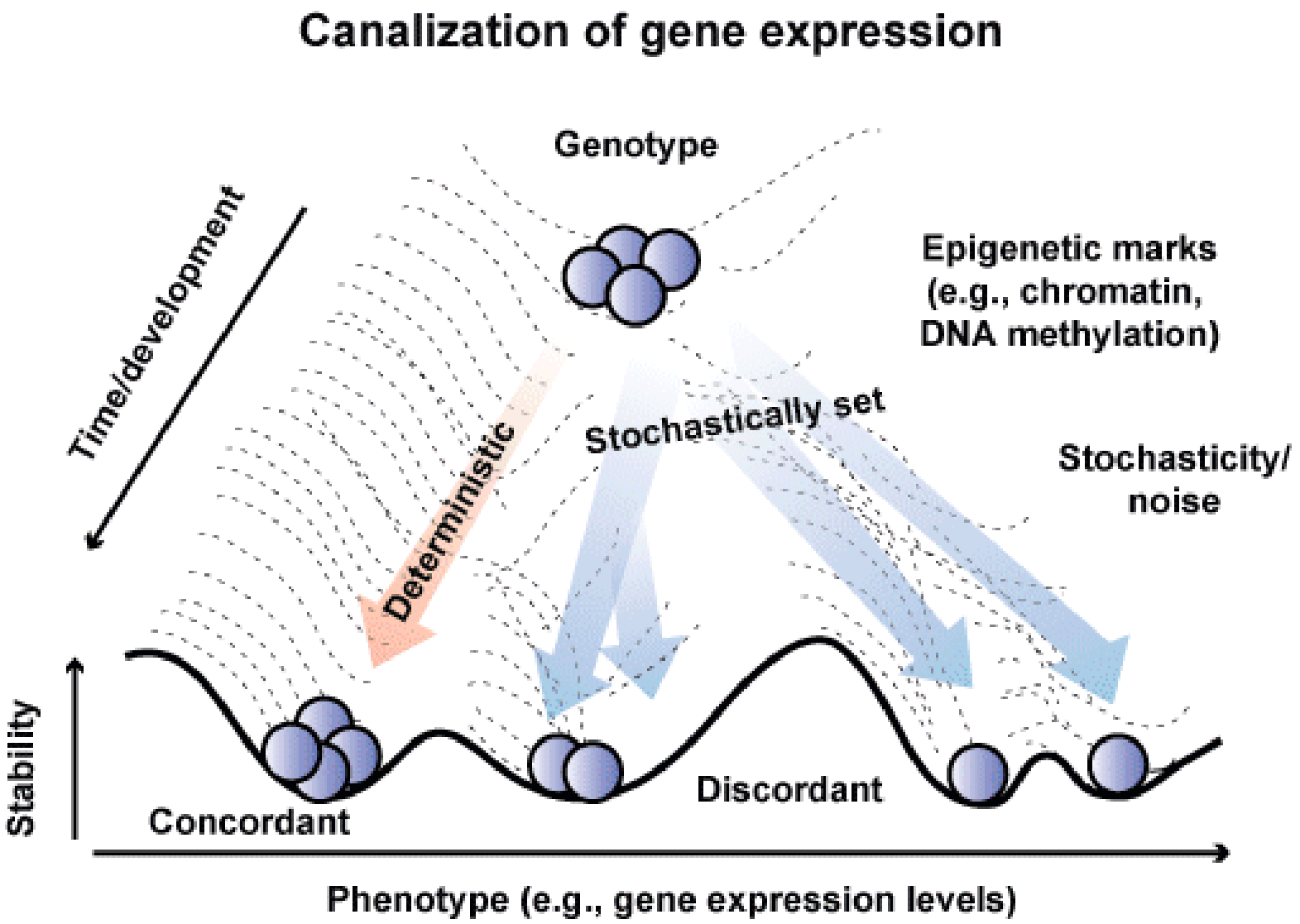
Loughry and McDonough (2013)

Dasypus hybridus

Fernandez (1909)

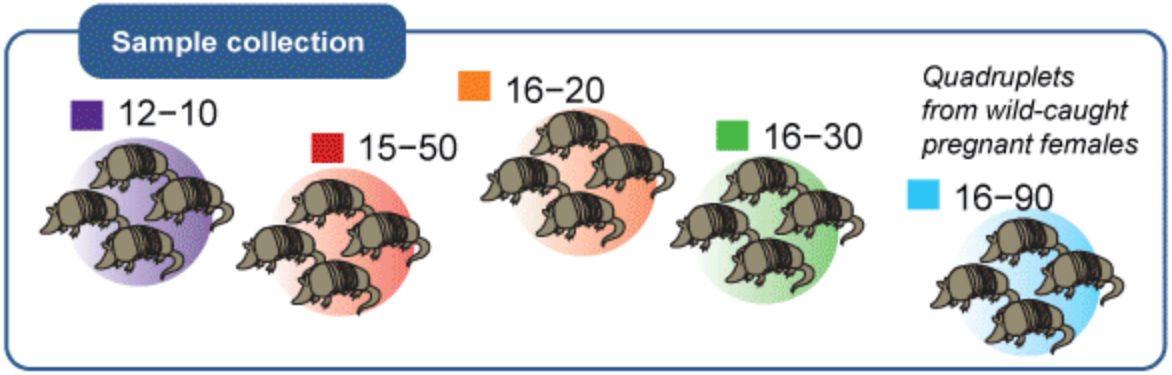
Chaetophractus villosus

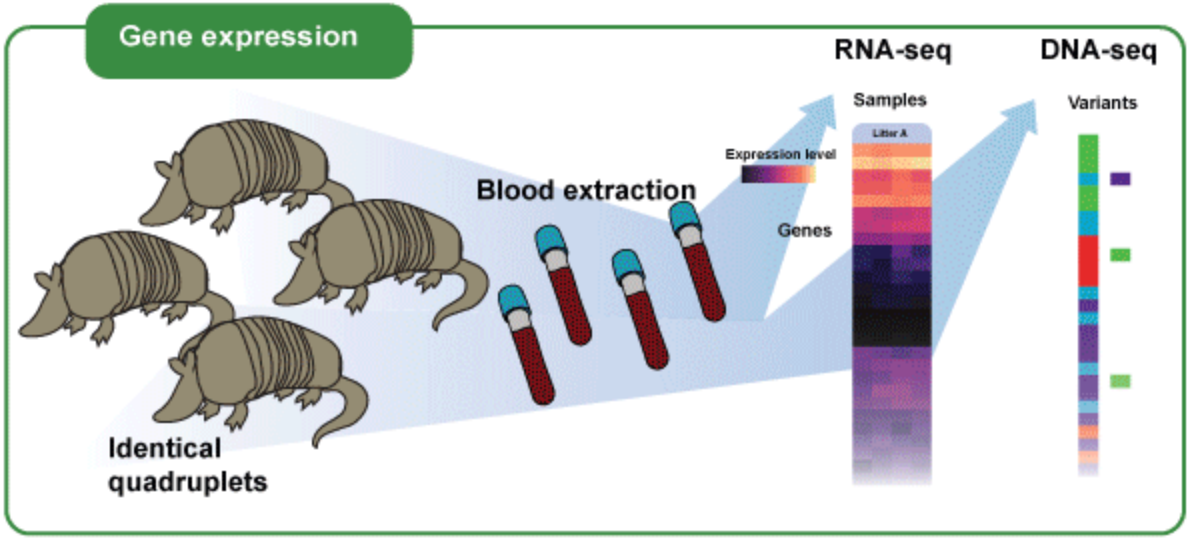
Newman (1917)



Waddington landscape

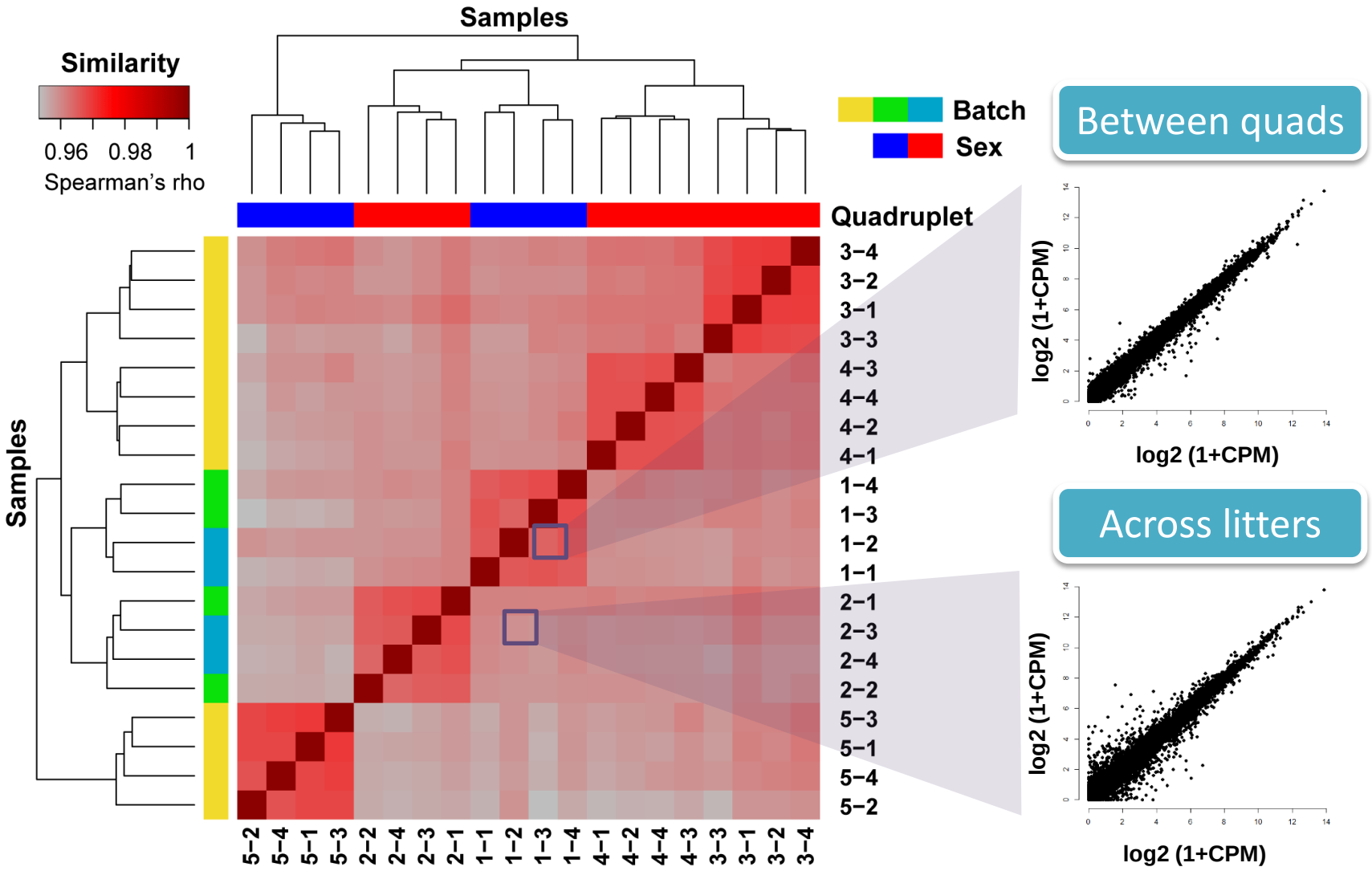
Data collection



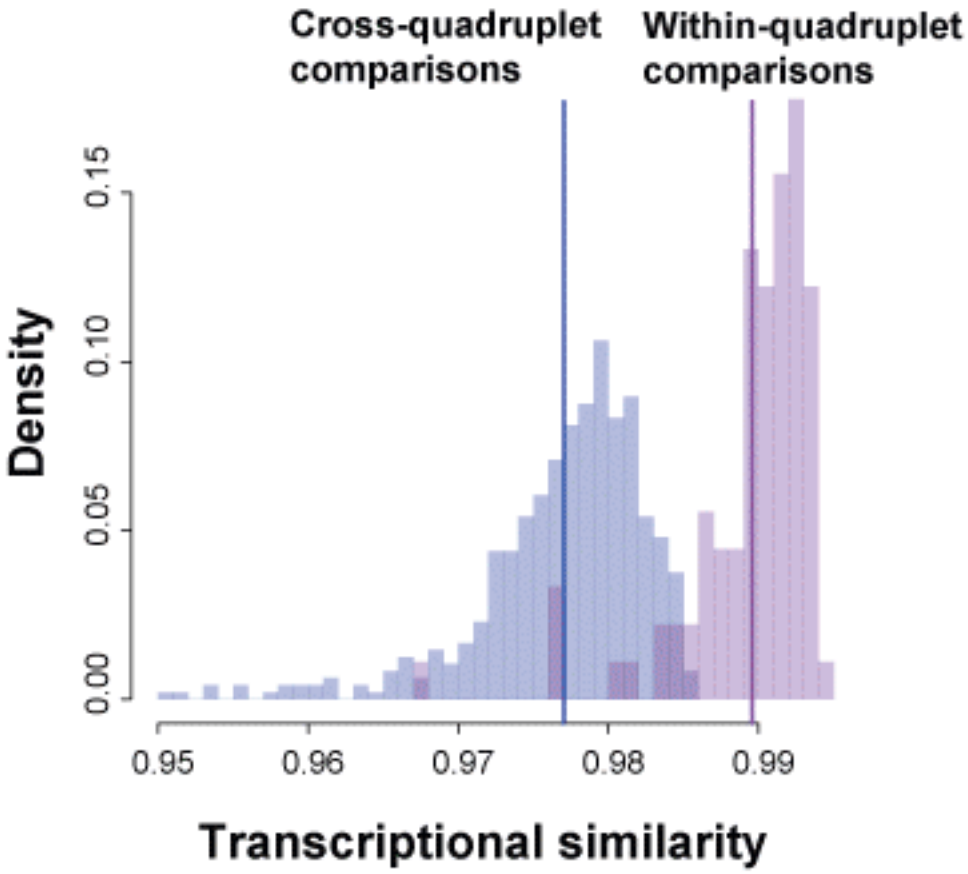


PBMCs at three time points over a year

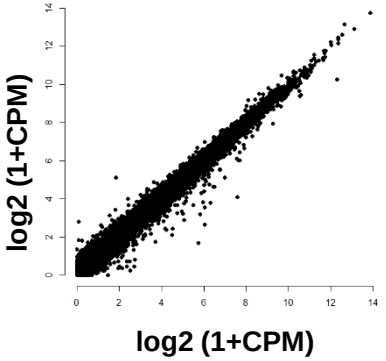
Higher transcriptional similarity within than across litters



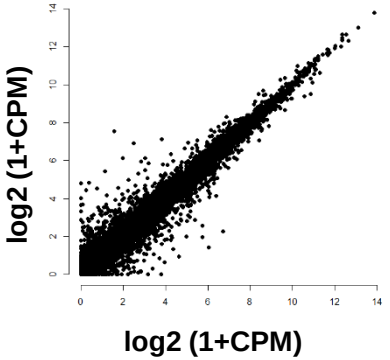
Higher transcriptional similarity within than across litters



Between quads



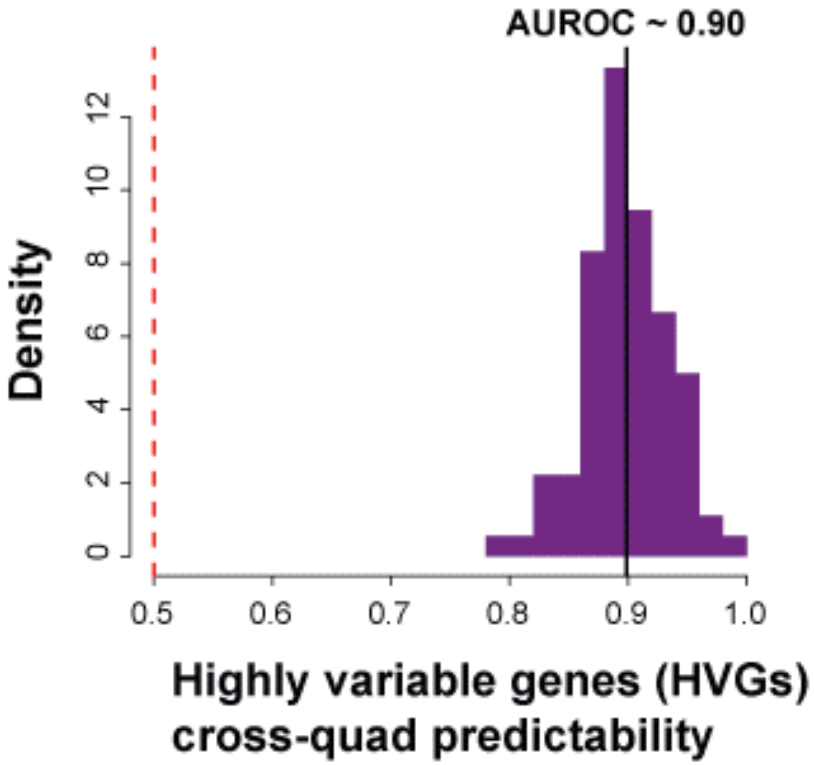
Across litters

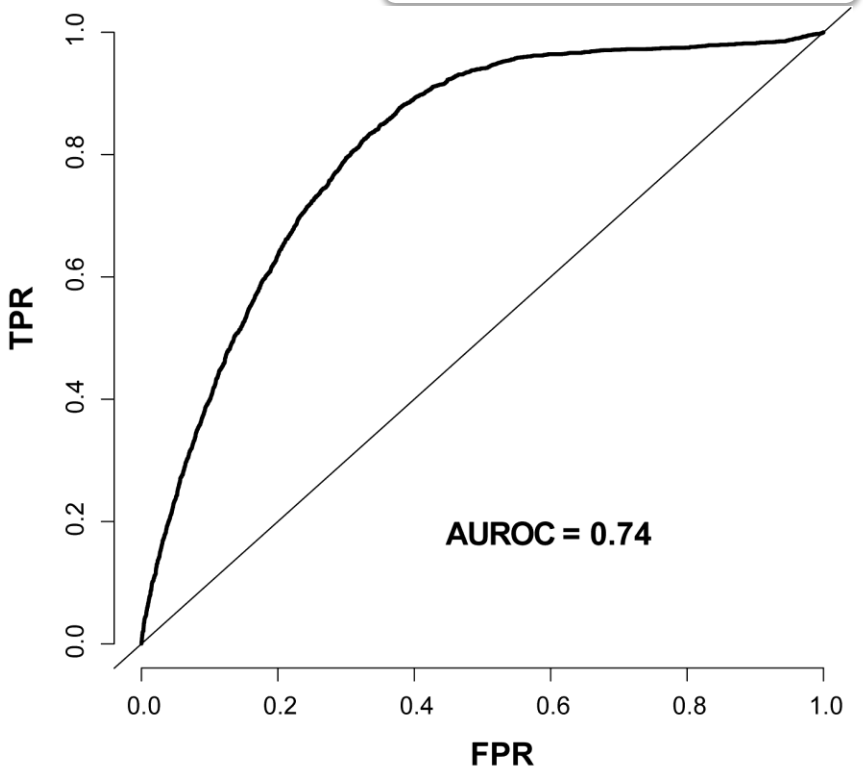


Stable genes are enriched for known human housekeeping genes

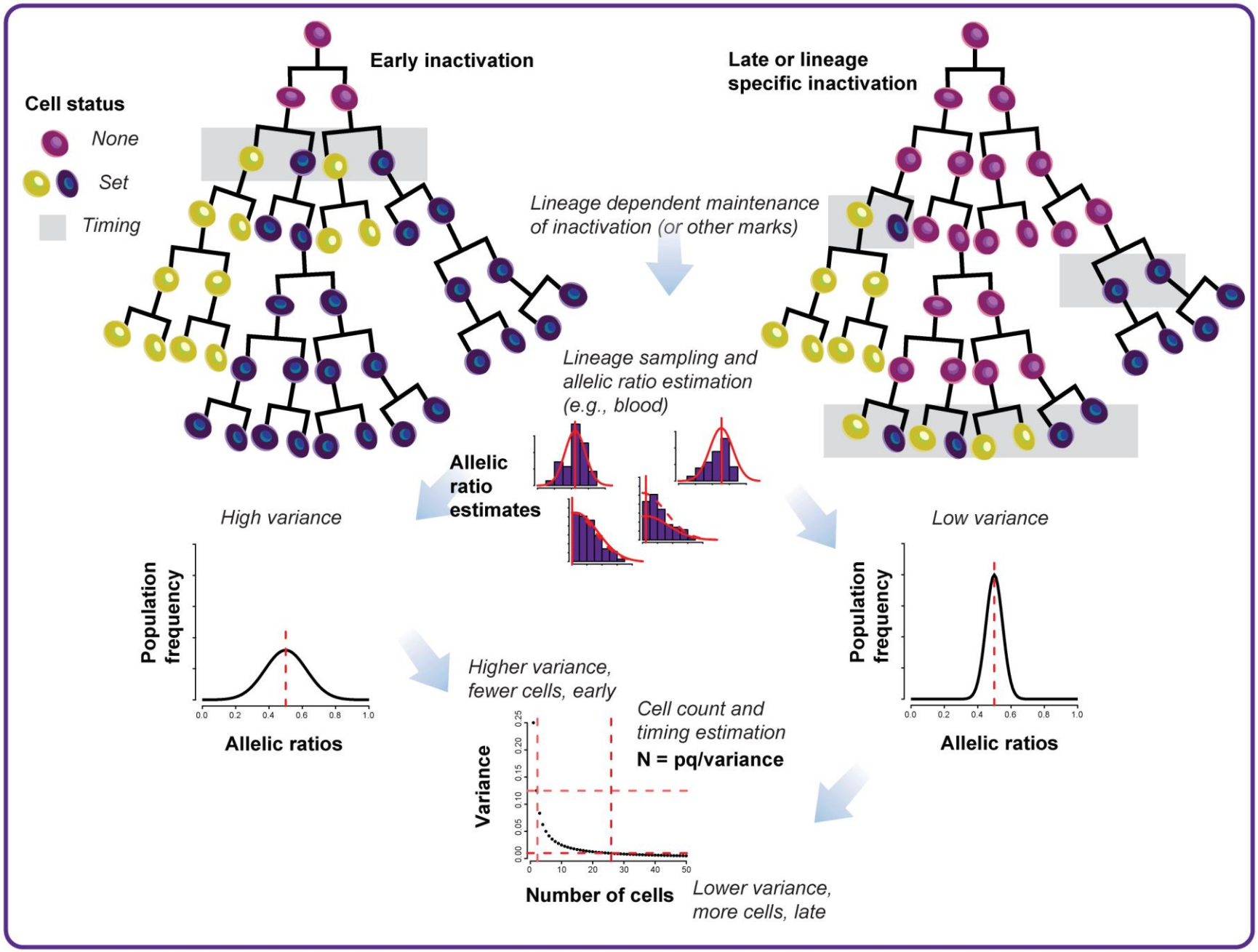
3804 human housekeeping genes

Eisenberg and Levanon 2013

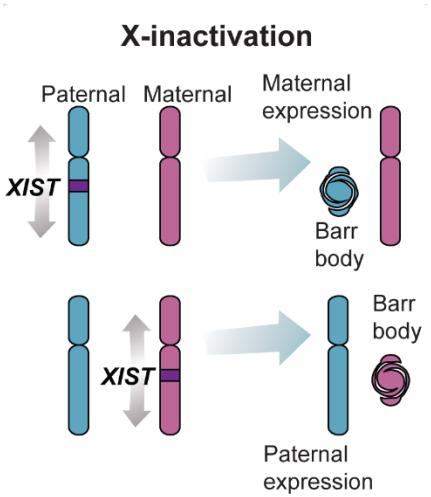




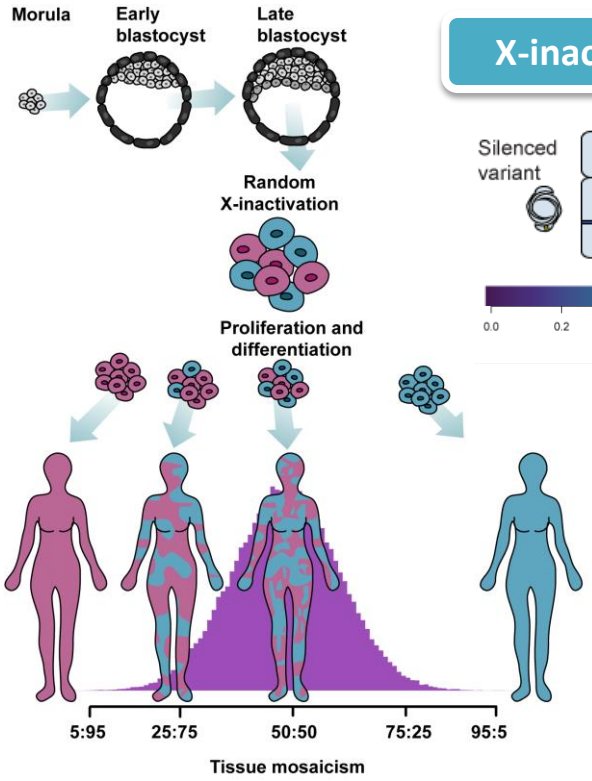
Estimating developmental timing of individuality



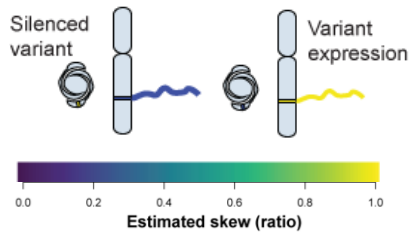
X-inactivation: canalized intrinsic noise



X-skewing ratios

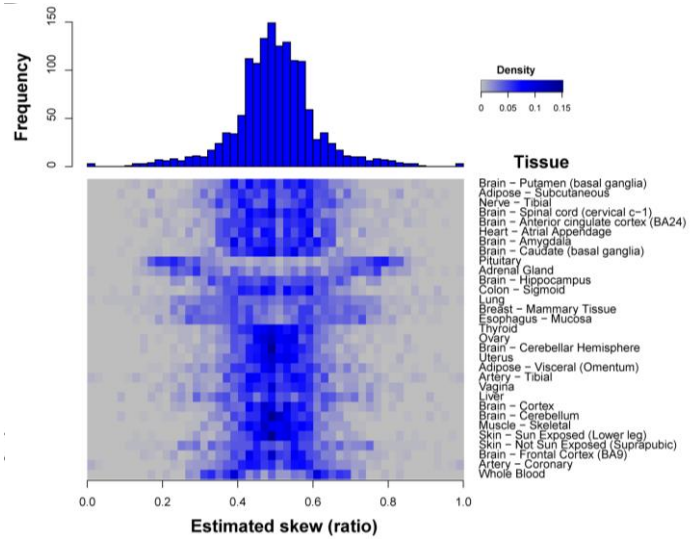


X-inactivation assays

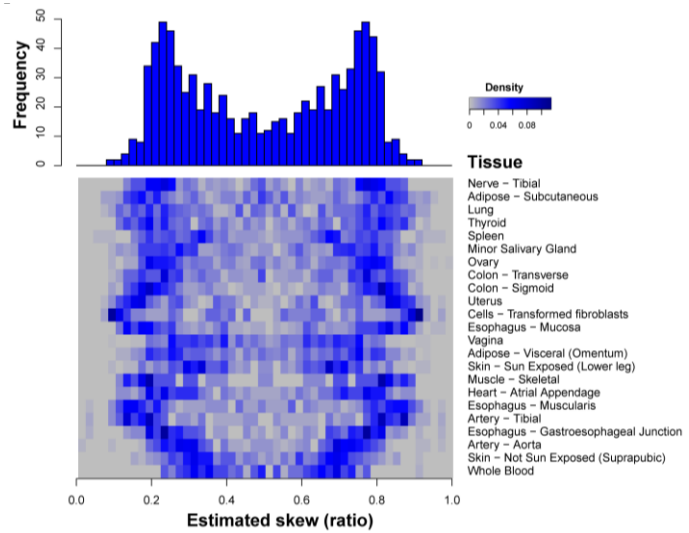


Variation in human X-inactivation within an individual across tissues

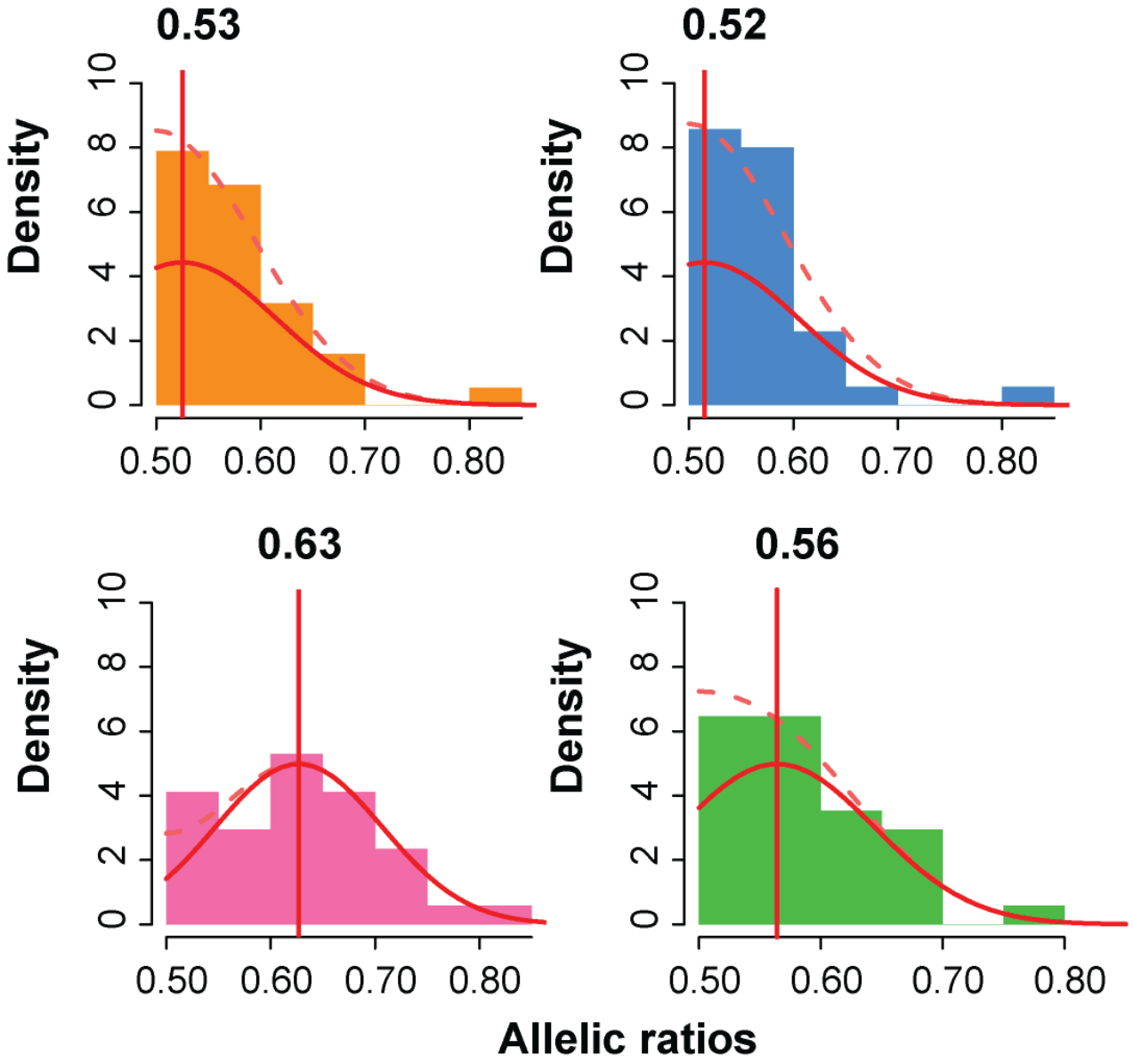
Random X-inactivation



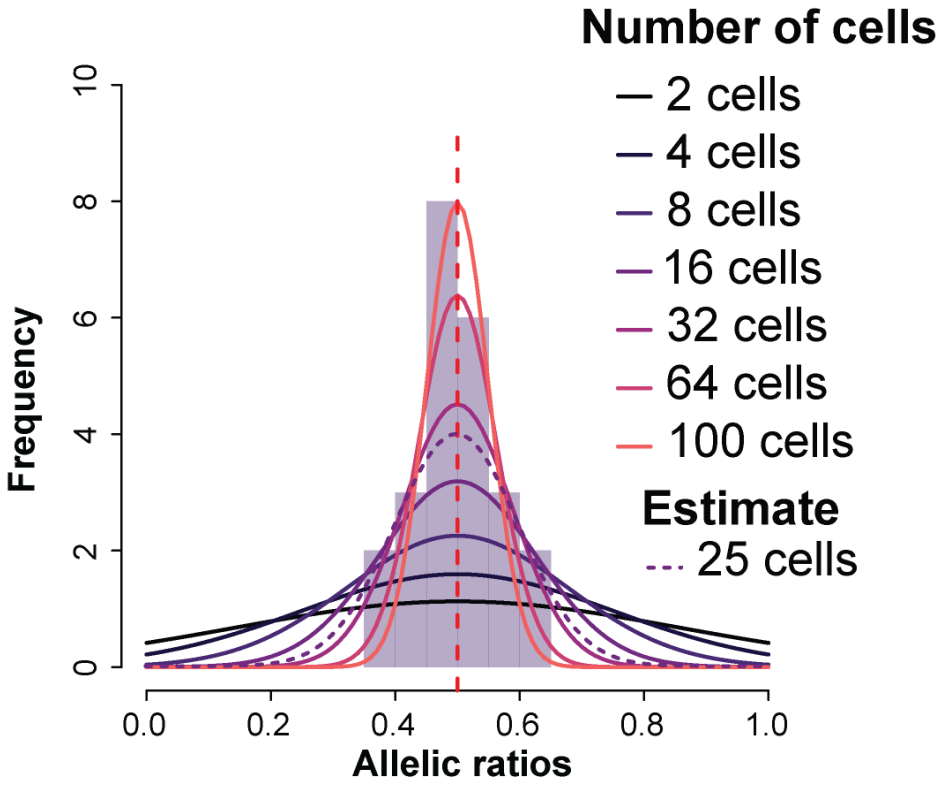
Skewed X-inactivation

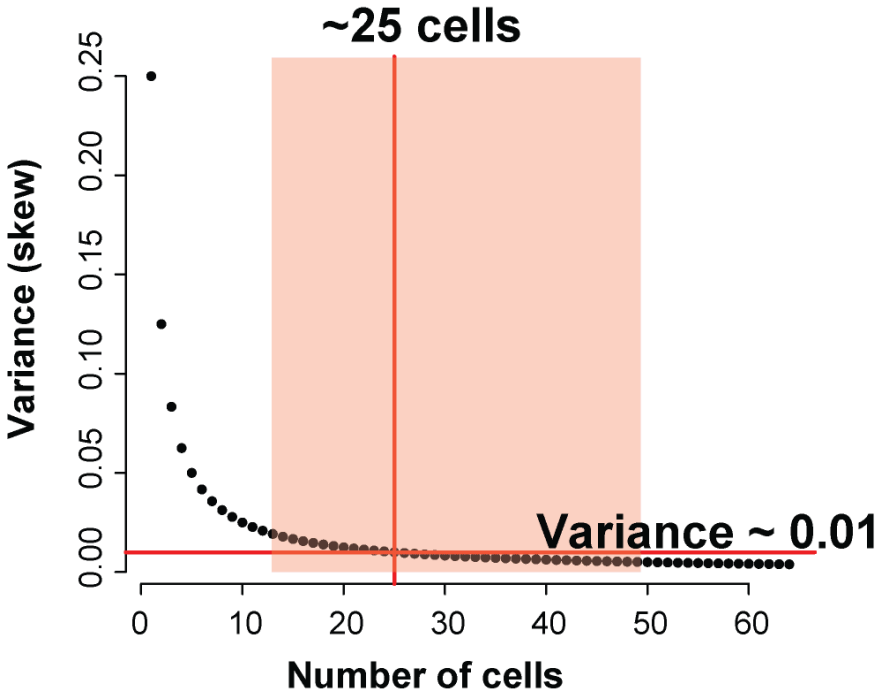


Individual armadillo X-inactivation ratios

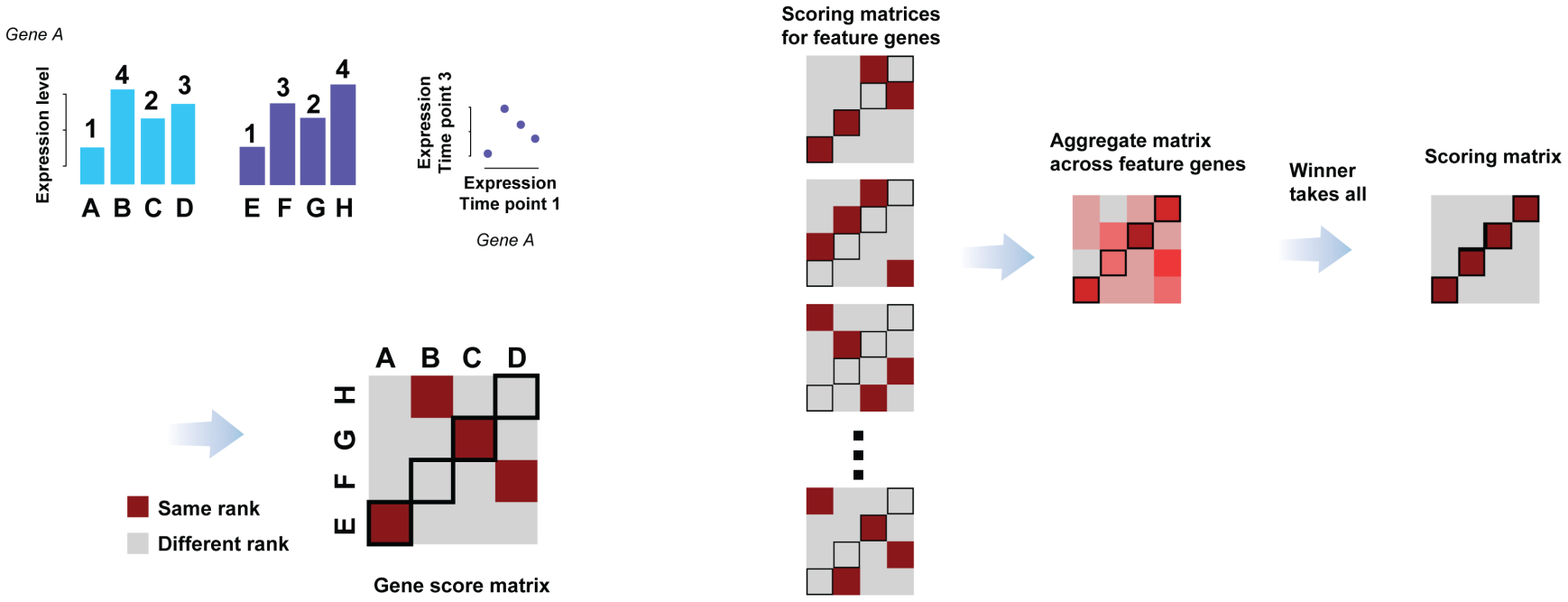


~25 cells in the initial population

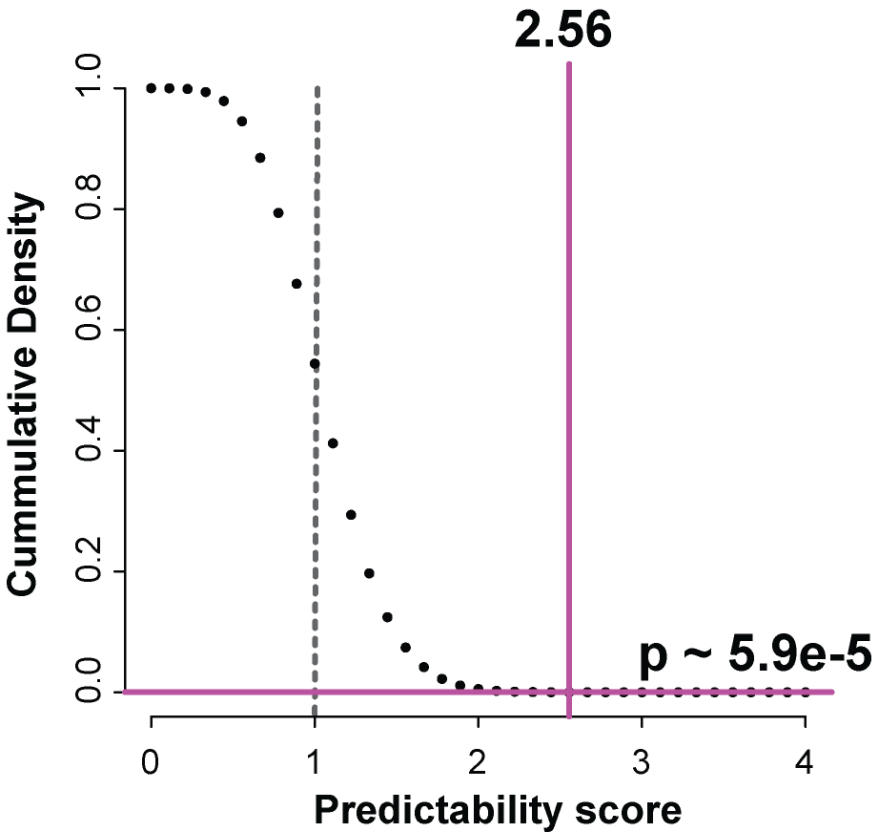


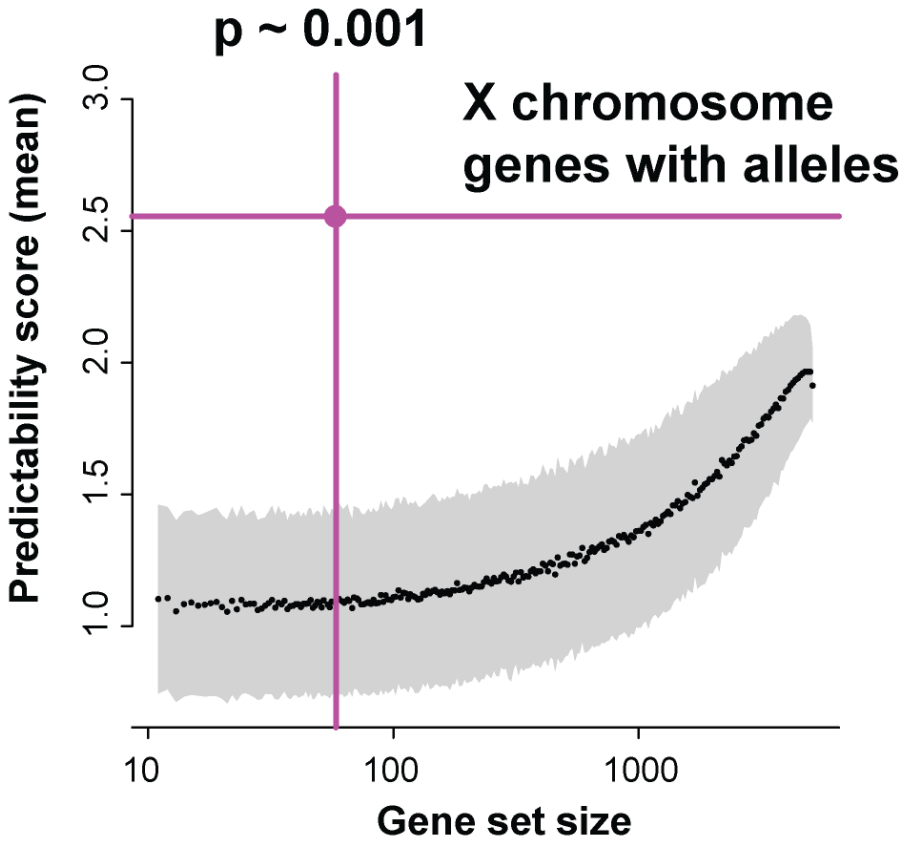


Predicting identity

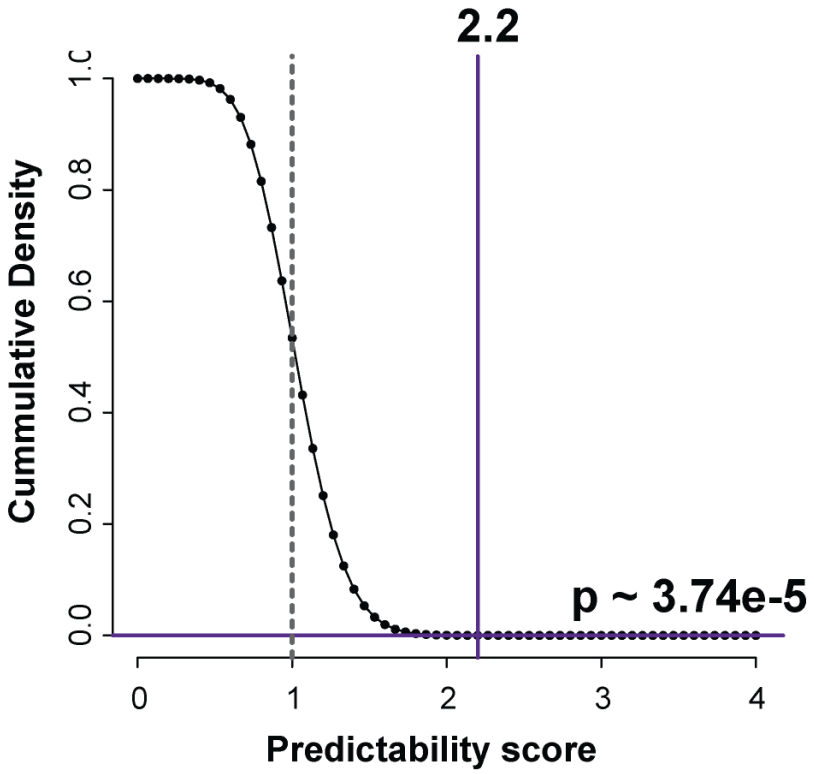


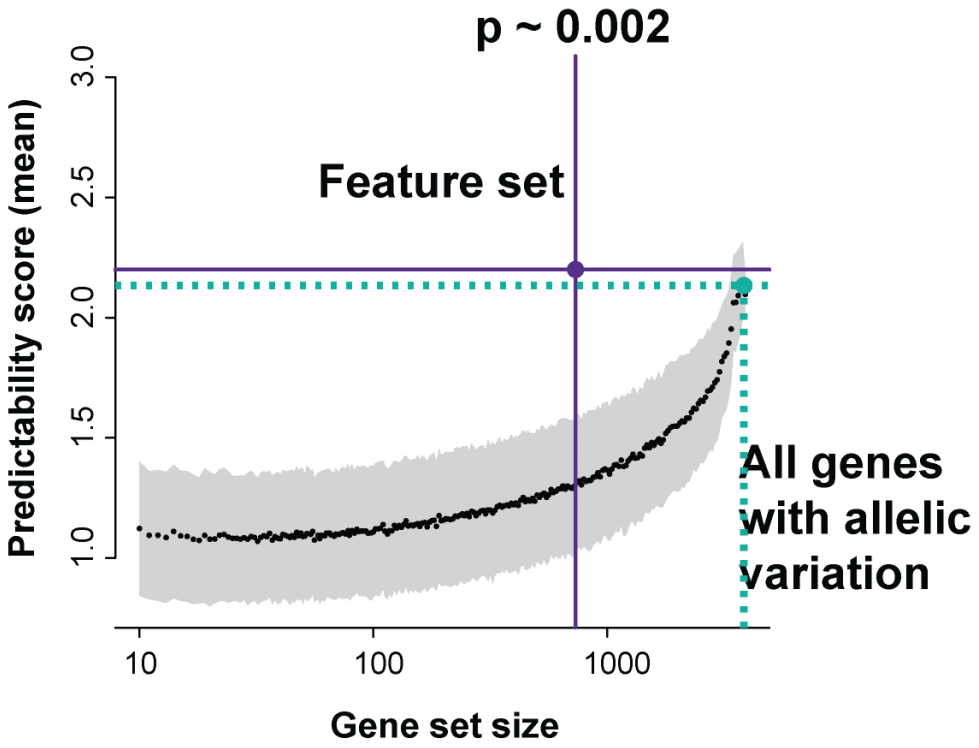
X-skew predicts identity



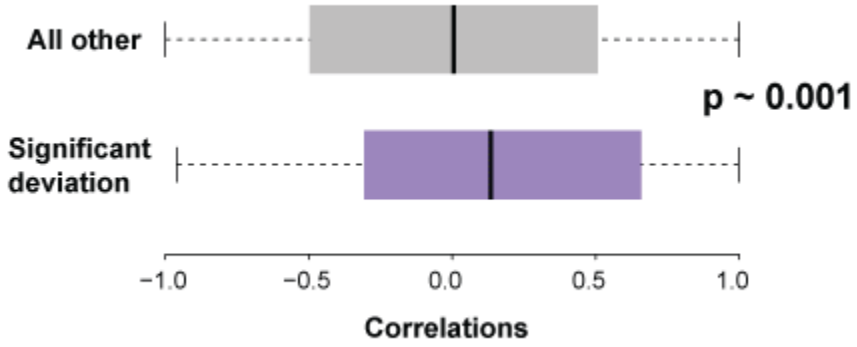


Canalized intrinsic noise marks lineage

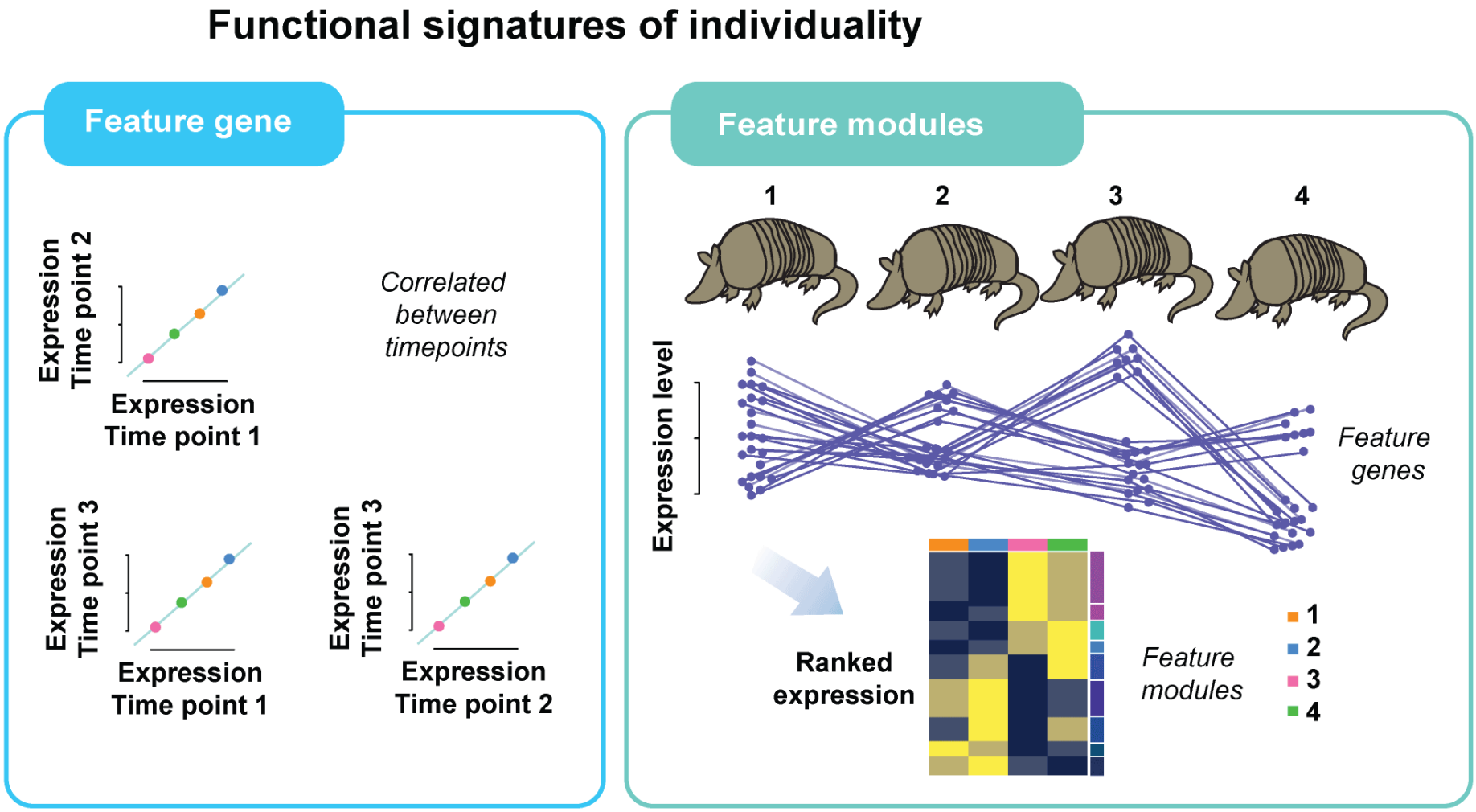




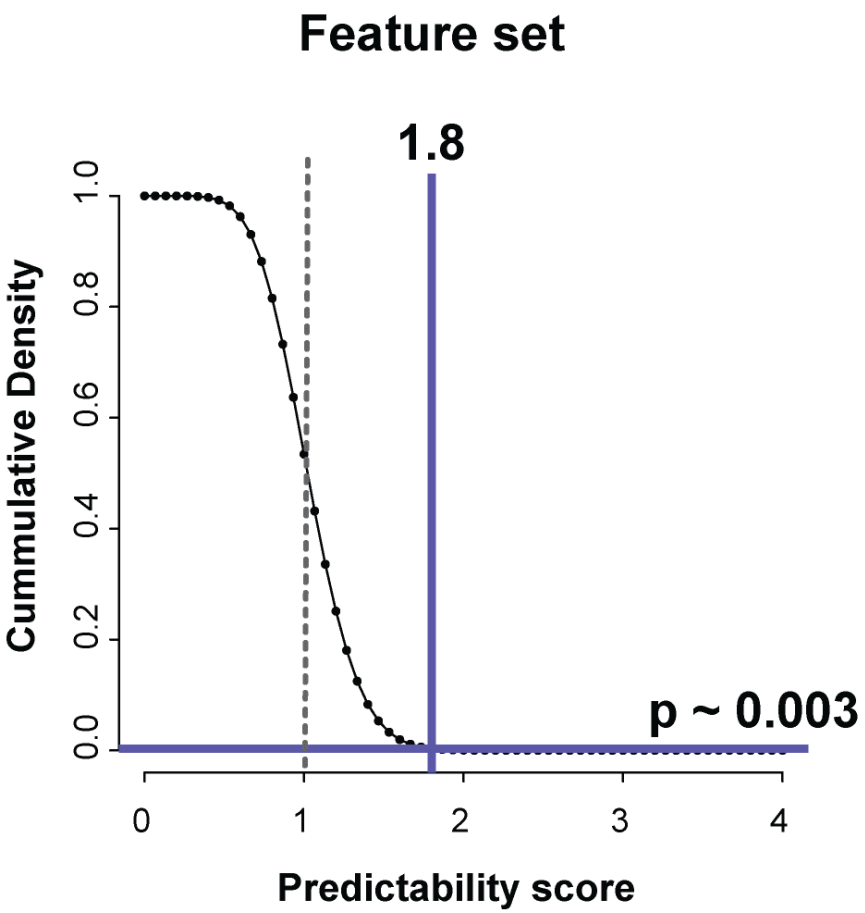
Genes don't overlap so not likely to be X related. Also, in males.

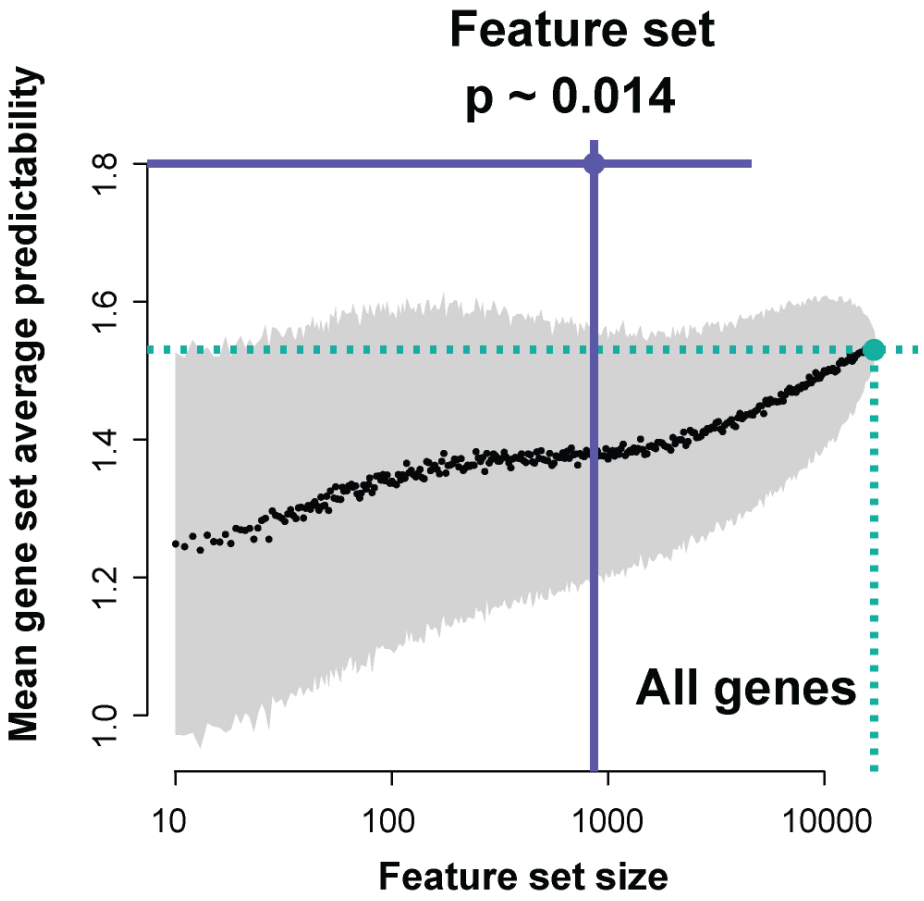


Extrinsic noise

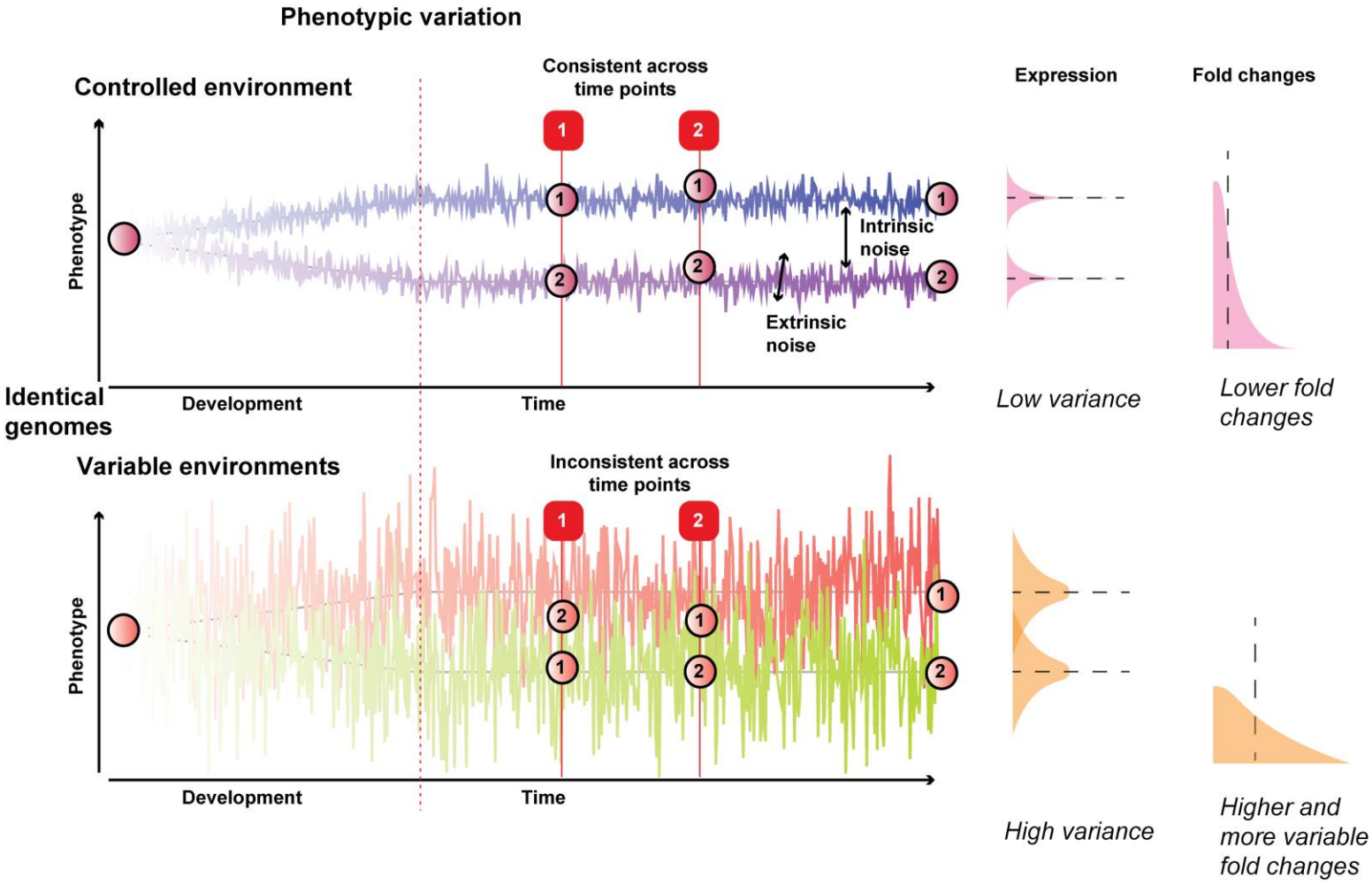


Canalized extrinsic noise predicts identity

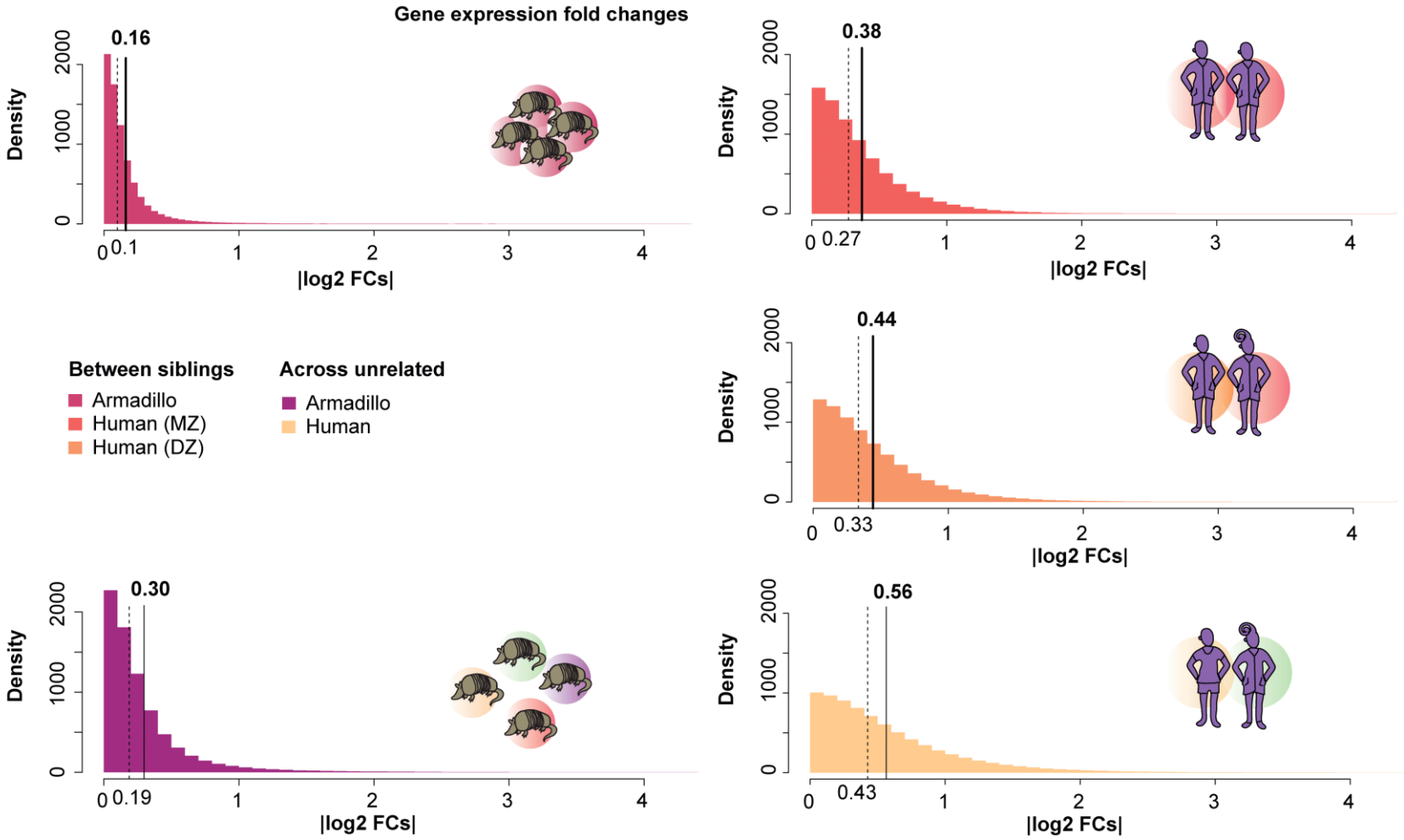




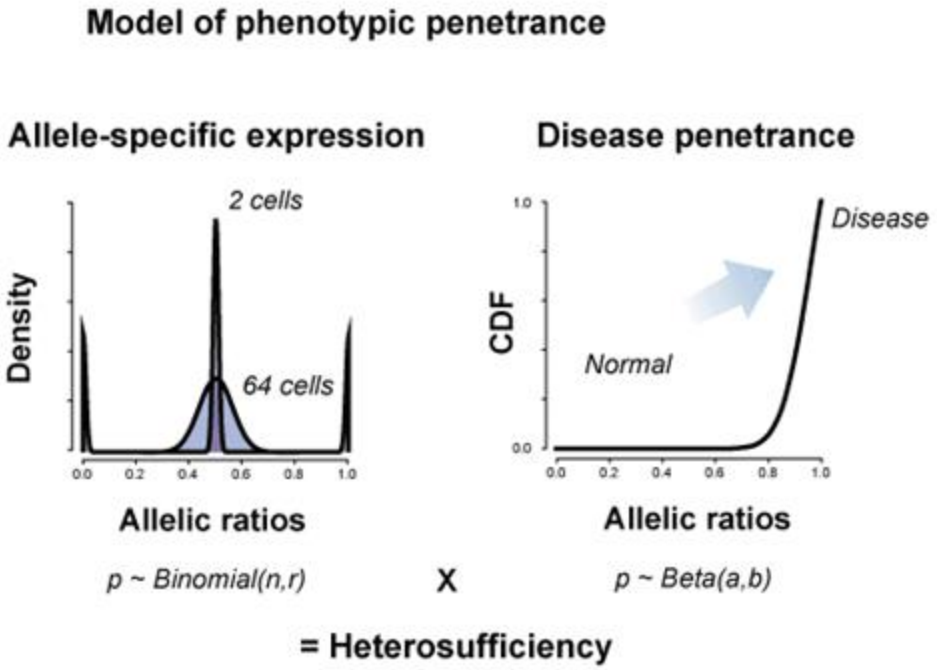
Revisiting: Why armadillos?

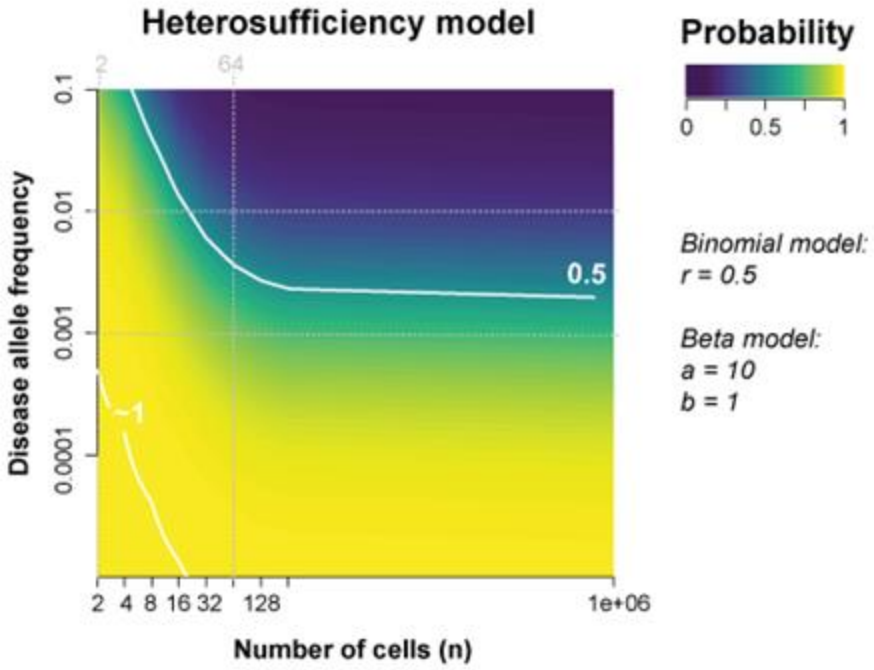


Suppression of environmental noise



Why this matters to disease:





Thanks

- Gillis lab
  - Sara Ballouz
  - Risa Kawaguchi
  - Megan Crow
  - Stephan Fischer
  - Manthan Shah
  - Ben Harris
  - Shaina Lu
  - Jonathan Werner
  - Nathan Fox
  - John Lee
  - Conor Cremin

- HRSA
  - Maria Pena
  - Linda Adams