

Frequency of mosaicism points
towards mutation prone early
cleavage cell divisions.

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Latifa Karim, Carole Charlier, Michel
Georges

Germ-line de novo mutations

- Definition:

Sequence variants absent in “incoming” gametes, present in “outgoing” gamete.



Germ-line de novo mutations

- Importance:

Source of genetic polymorphism

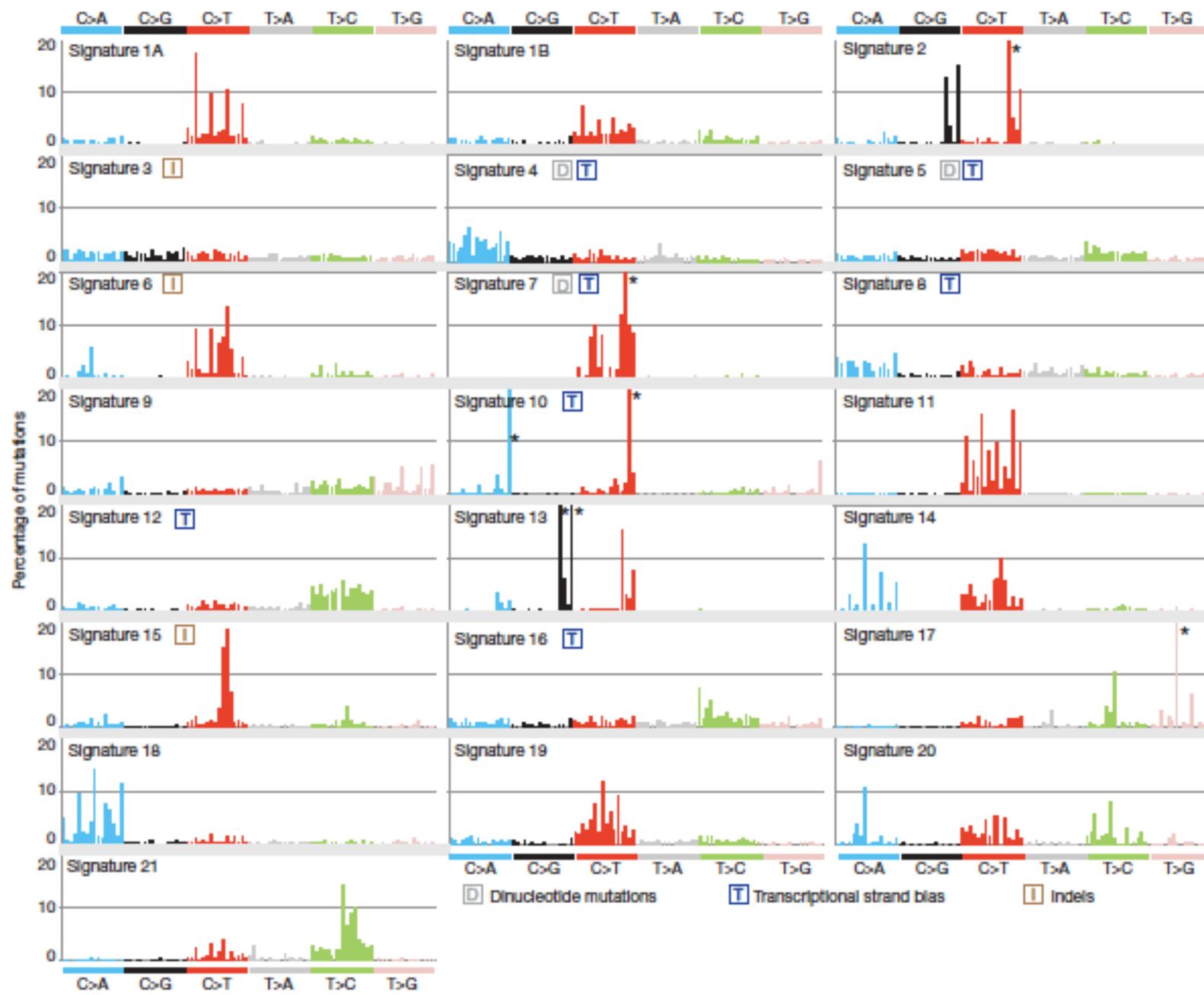
- Substrate for natural and artificial selection
- Cause of genetic diseases

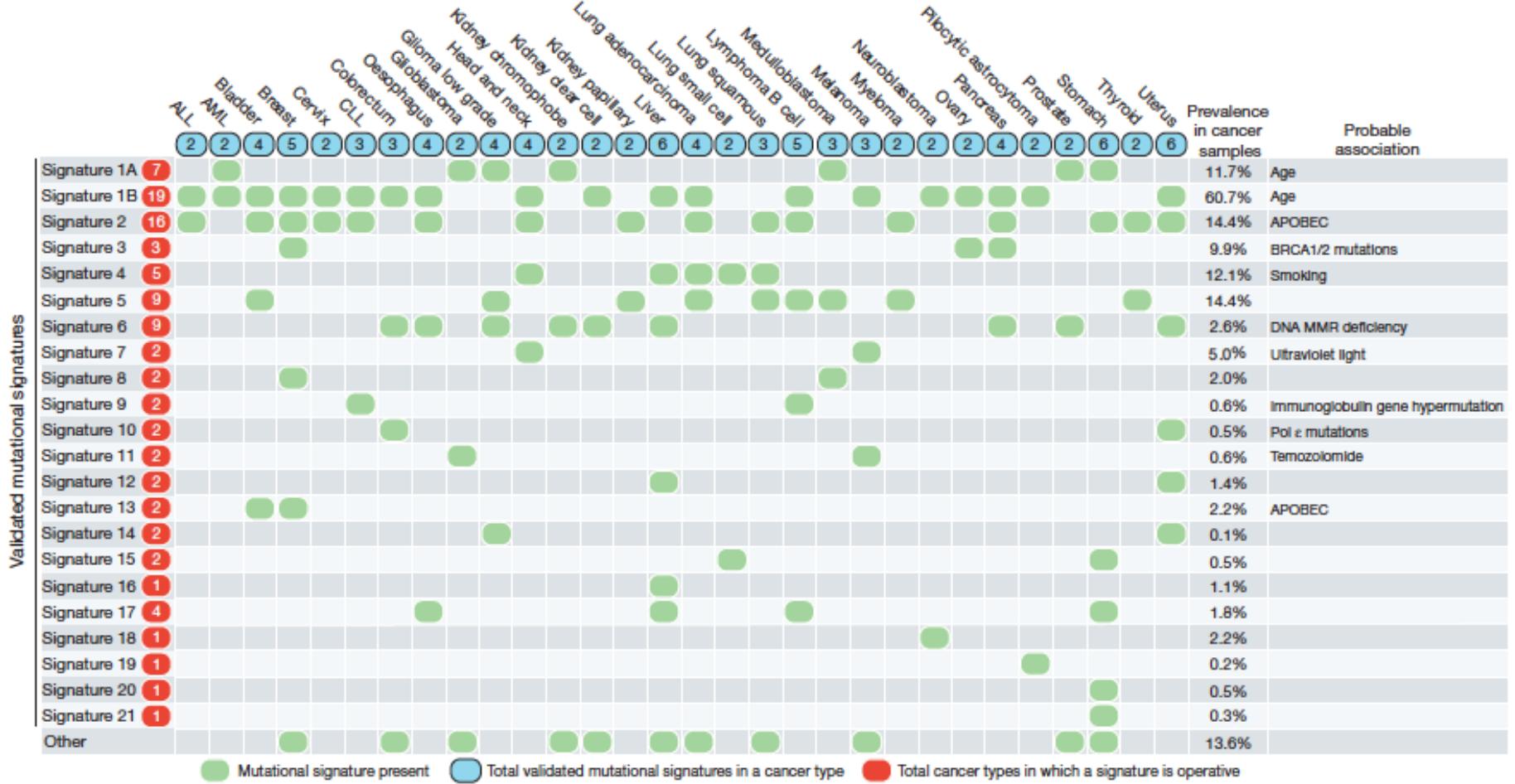
- Origin:

- Replication errors (cell-cycle-number dependent)
- DNA breakdown (time dependent)

Germ-line de novo mutations

- Variation:
 - Quantitative & qualitative
 - Sex (M>F), age (old > young)
 - Adaptation vs adaptability
- Measure:
 - Indirect (disease frequency, sequence divergence)
=> average
 - Direct (NGS) => individual

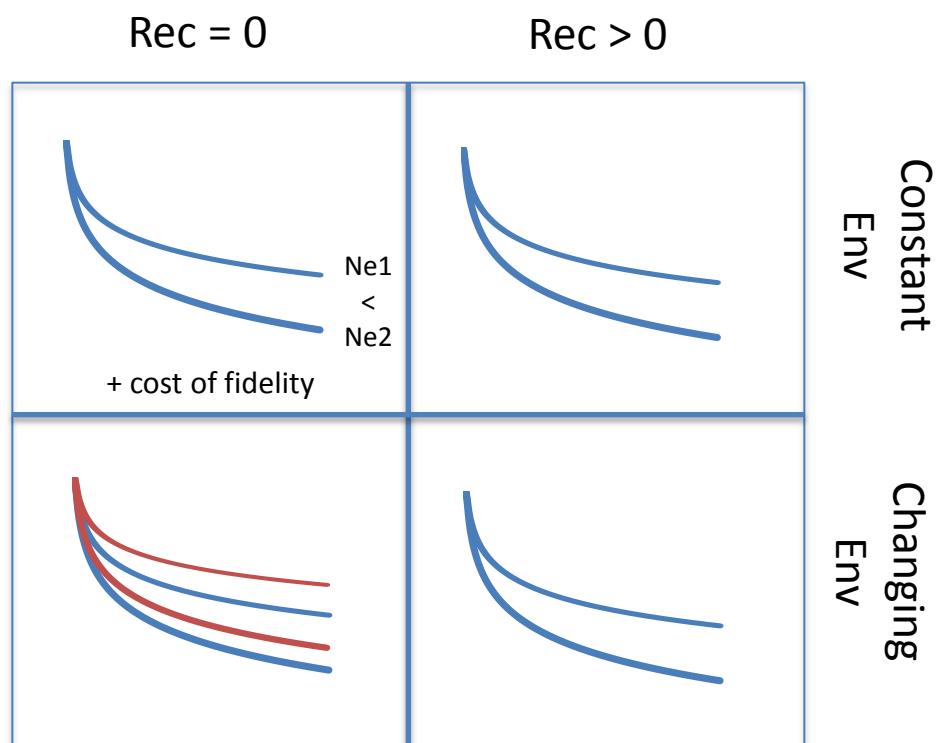
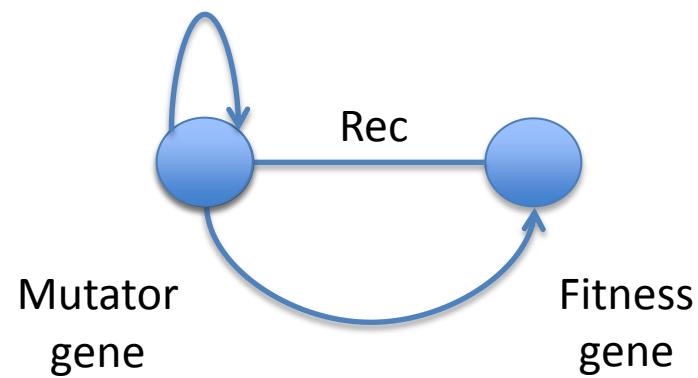




Germ-line de novo mutations

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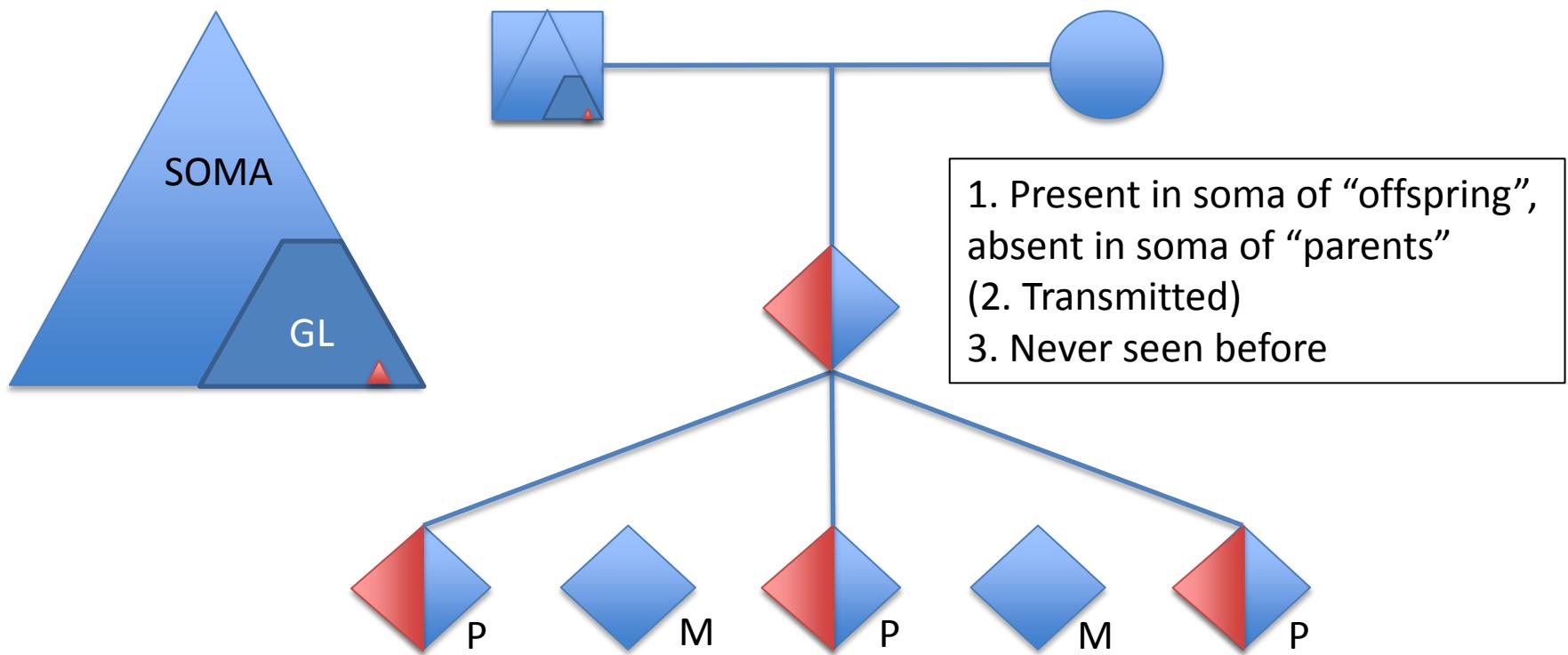
Adaptation vs adaptability



Germ-line de novo mutations

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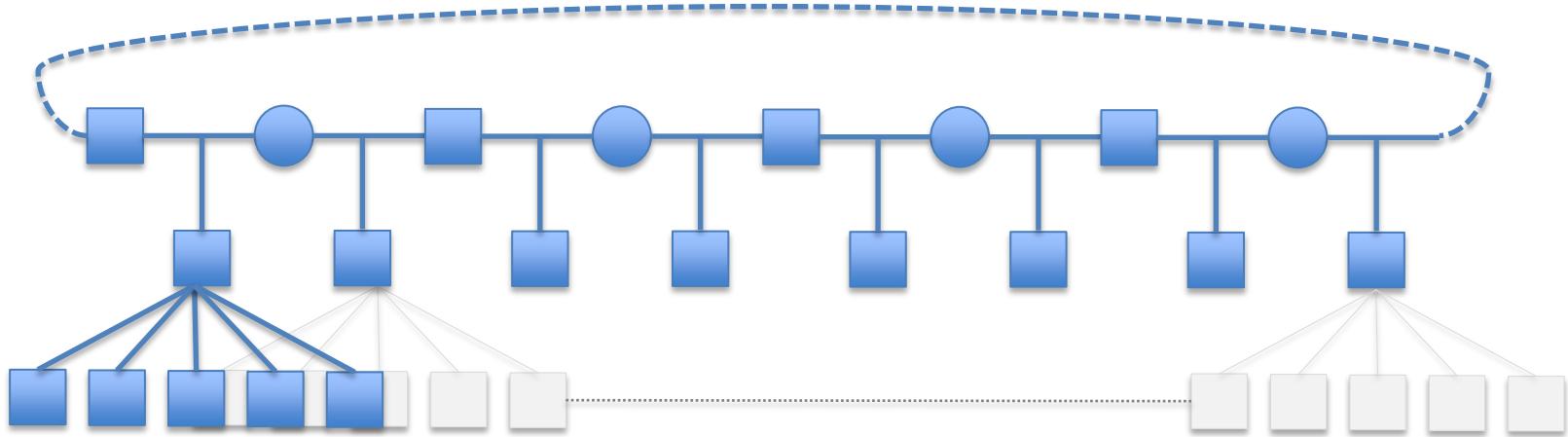
Standard direct measure



Estimated mutation rate



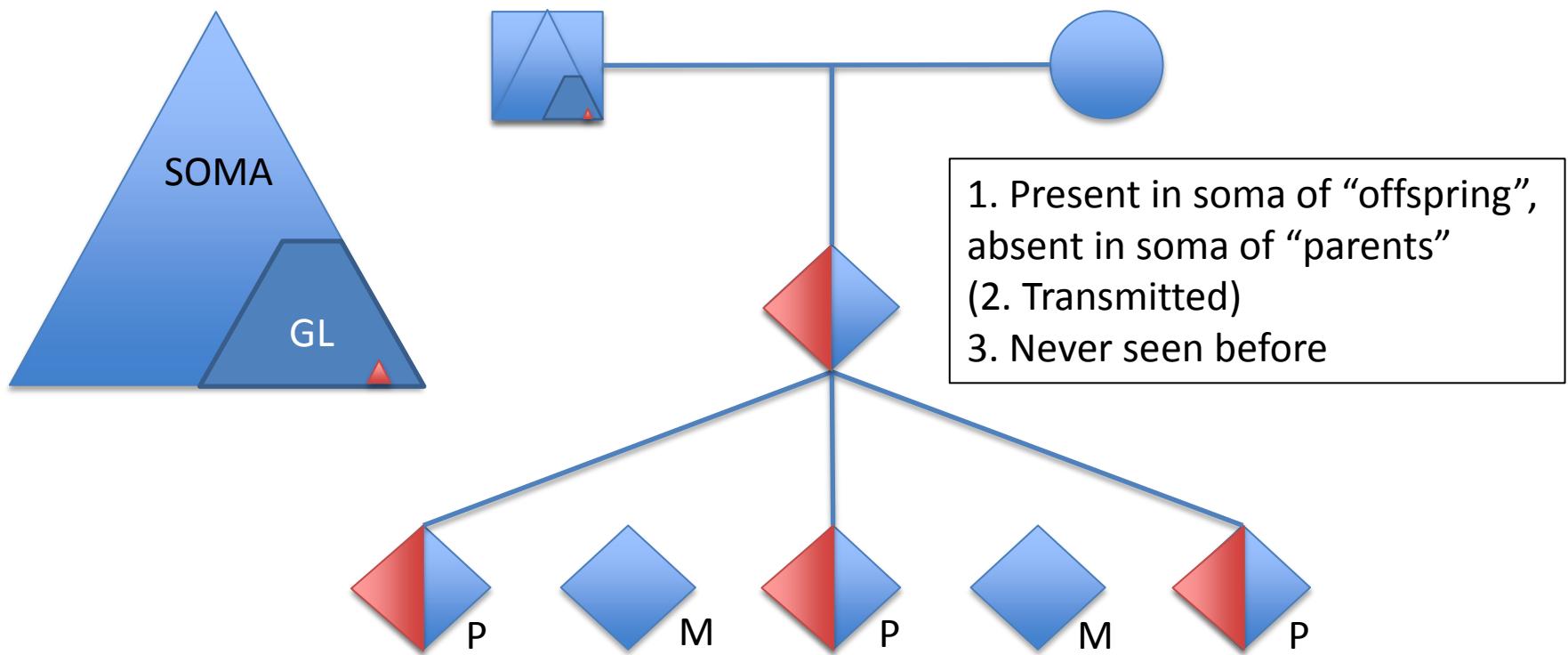
Damona – partim I



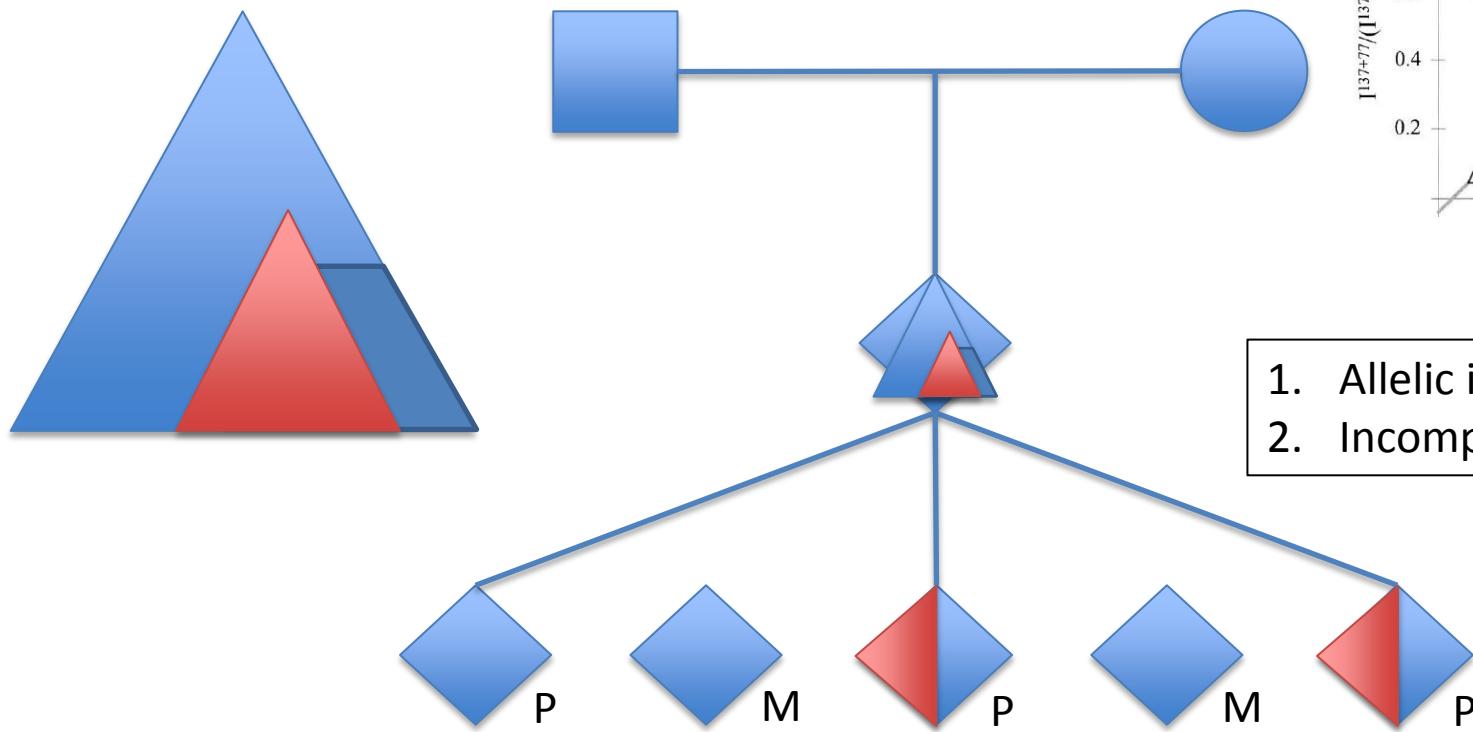
800 lanes
20 & 2-fold depth
M: sperm – F: blood
~ 150 sperm cells
~ 150 oocytes

11 / 01 /2015
~ 3/4 completed

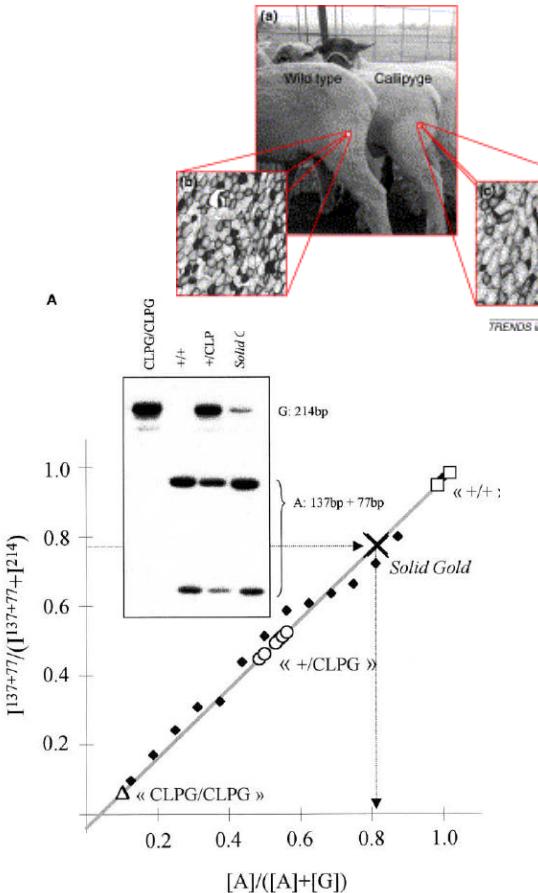
Standard direct measure



Mosaicism in the proband

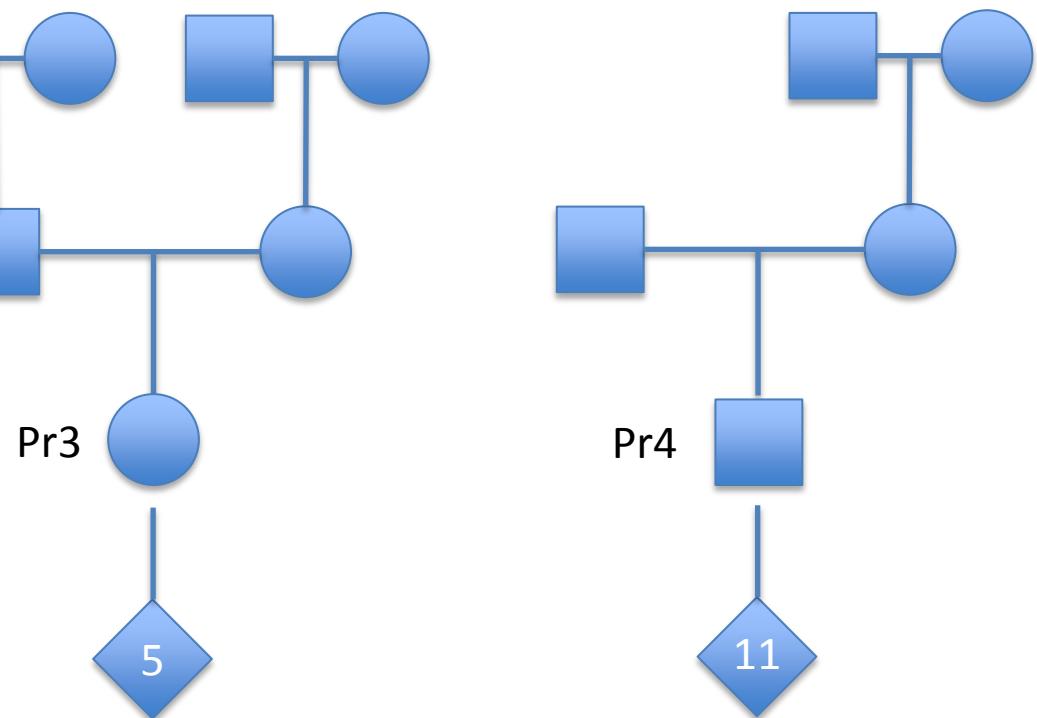
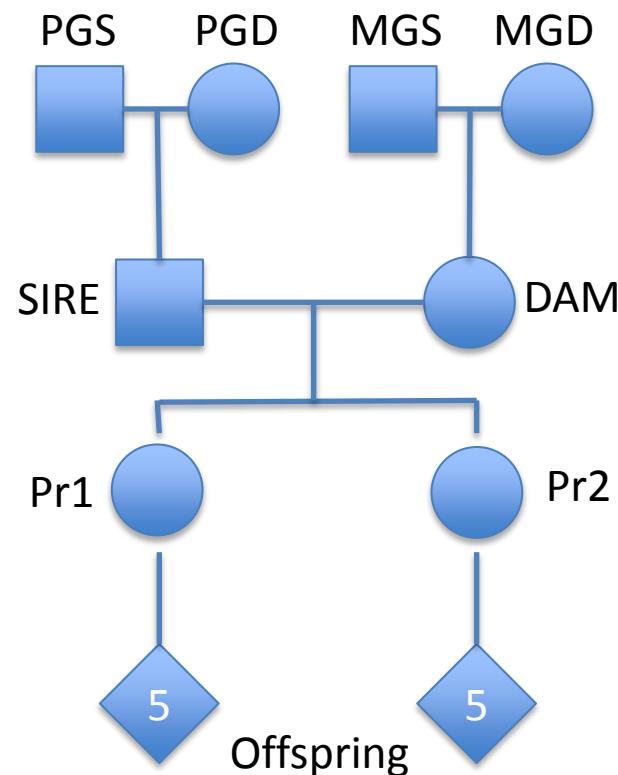


1. Allelic imbalance
2. Incomplete linkage

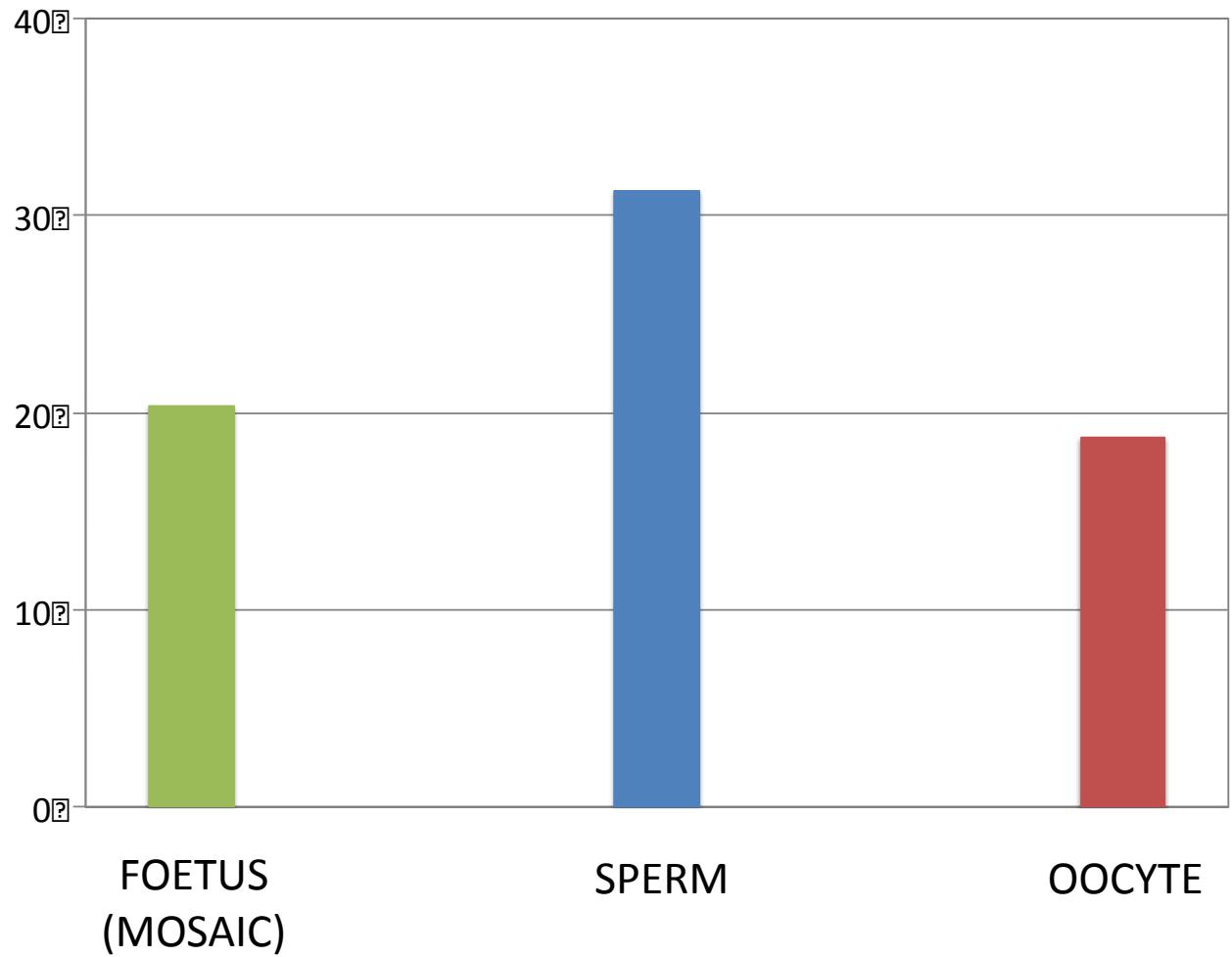
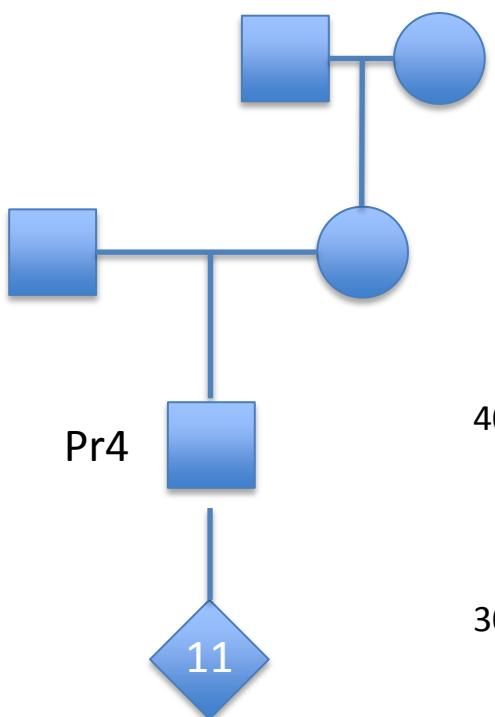


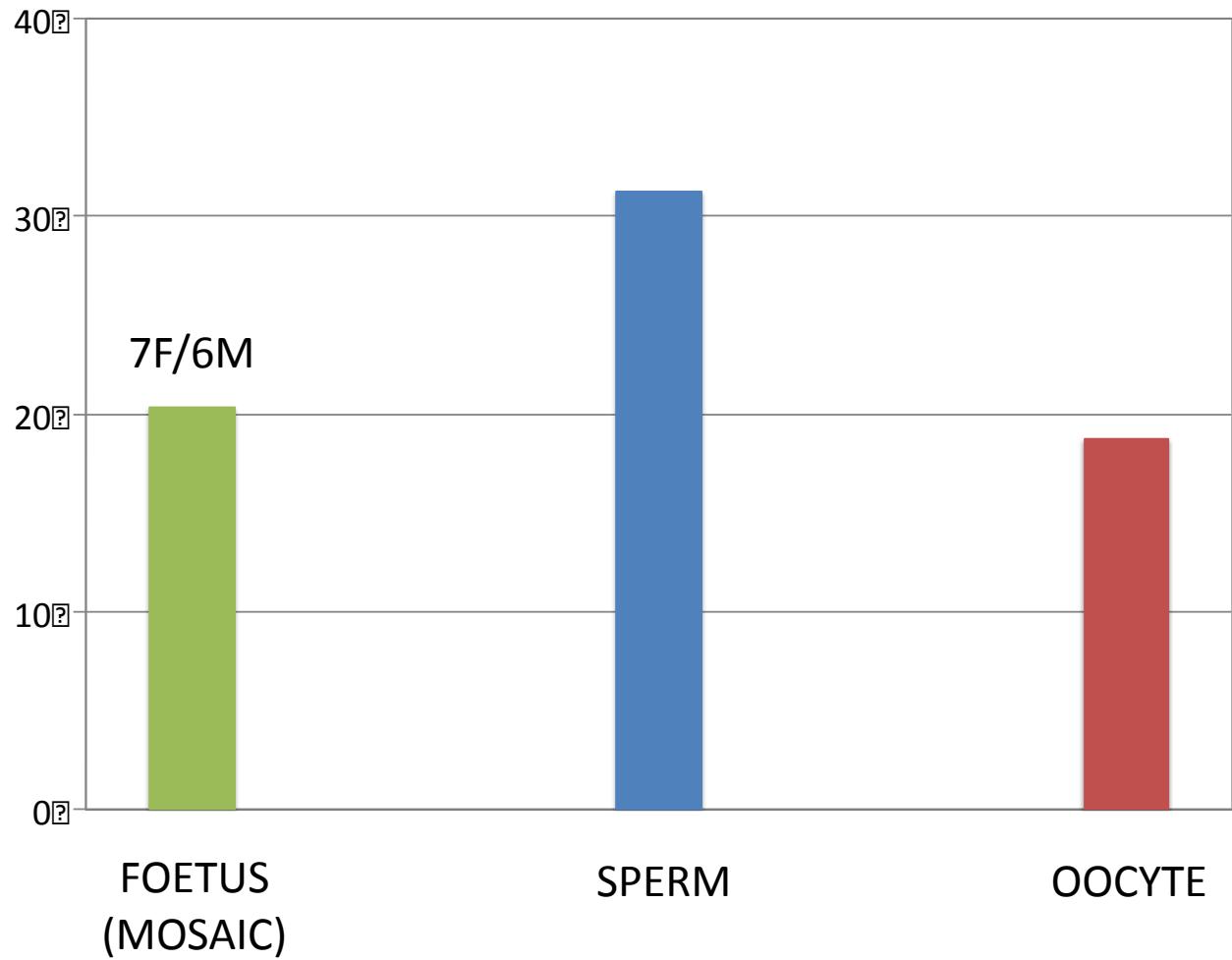
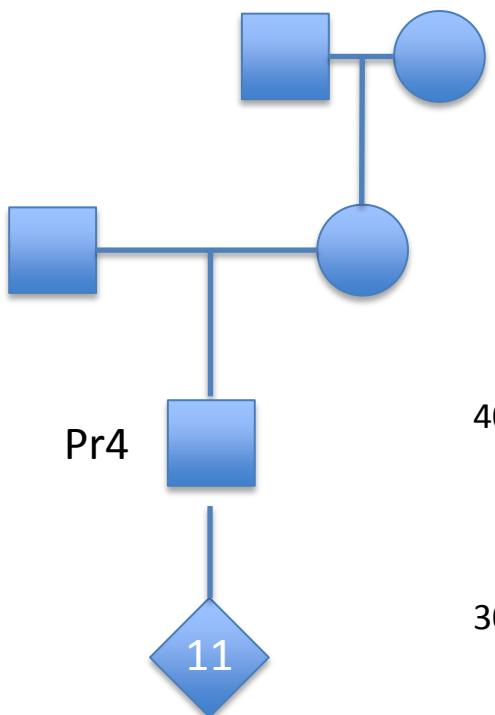
TRENDS in

Unique pedigrees

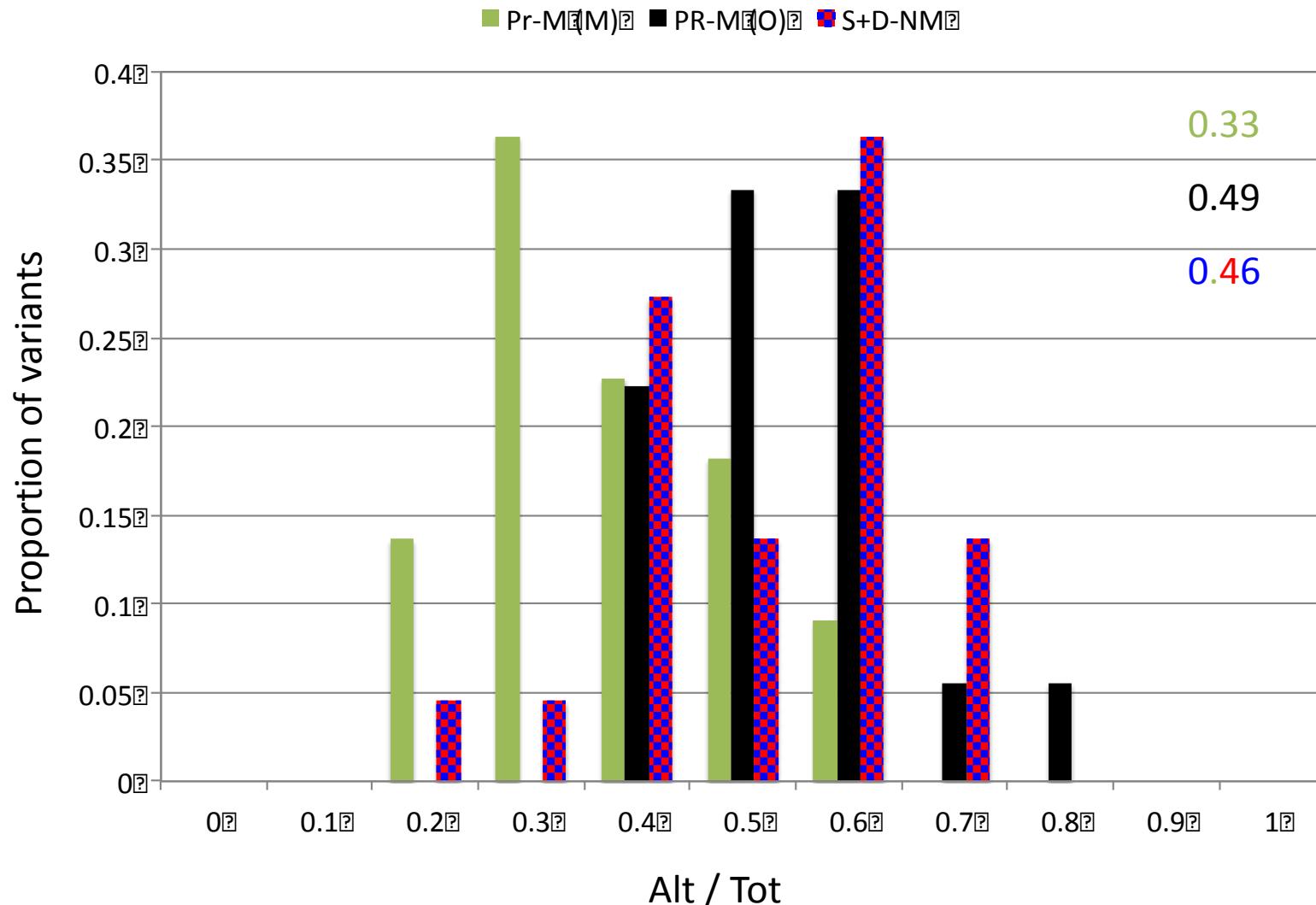


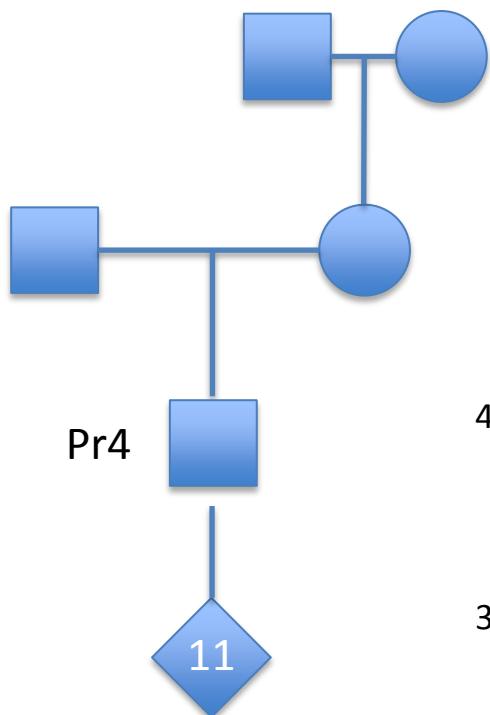
All individuals sequenced at ≥ 20 -fold depth



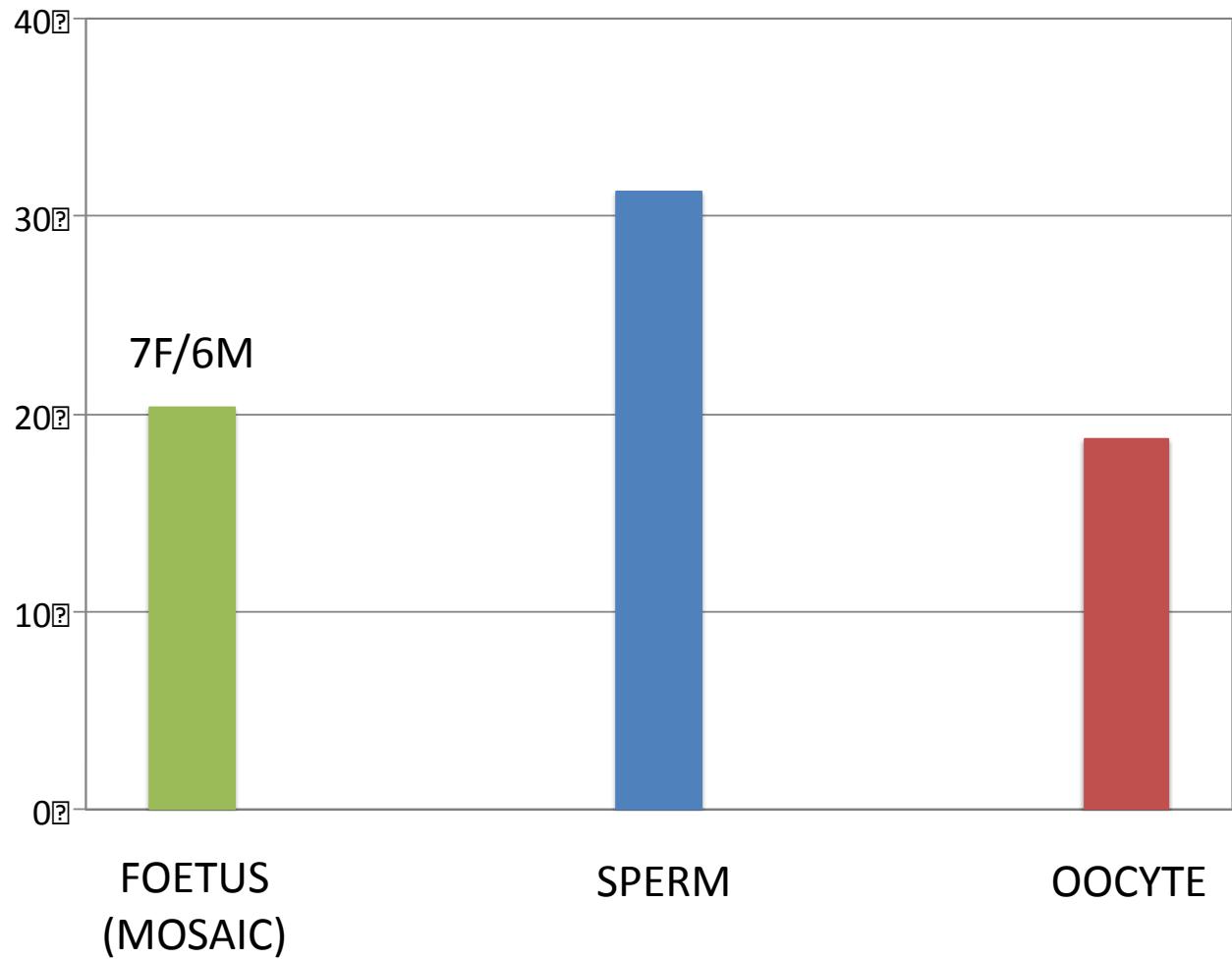


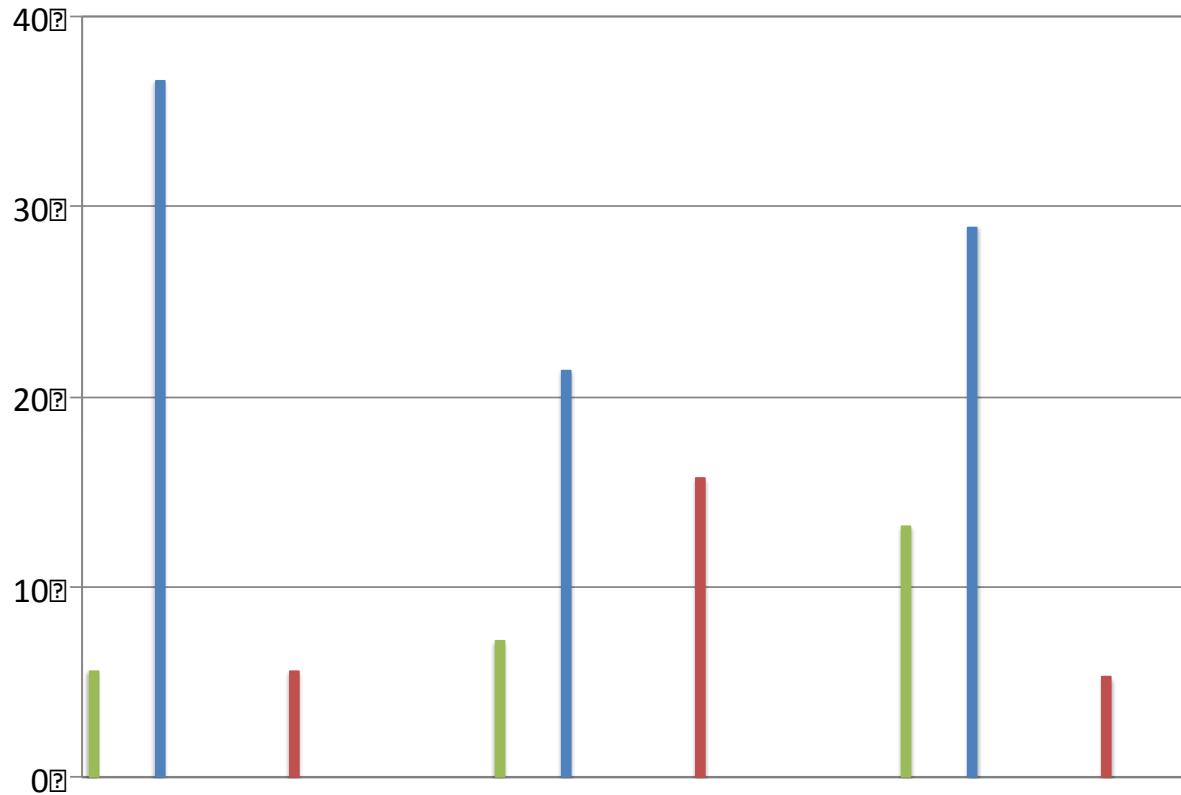
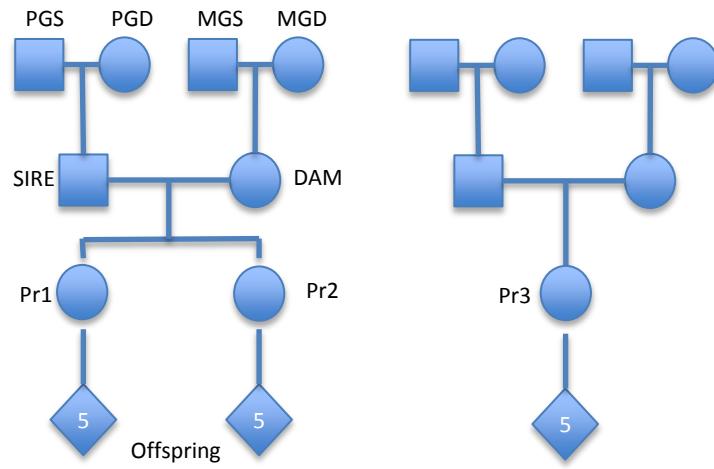
Allelic ratio de novo mutations

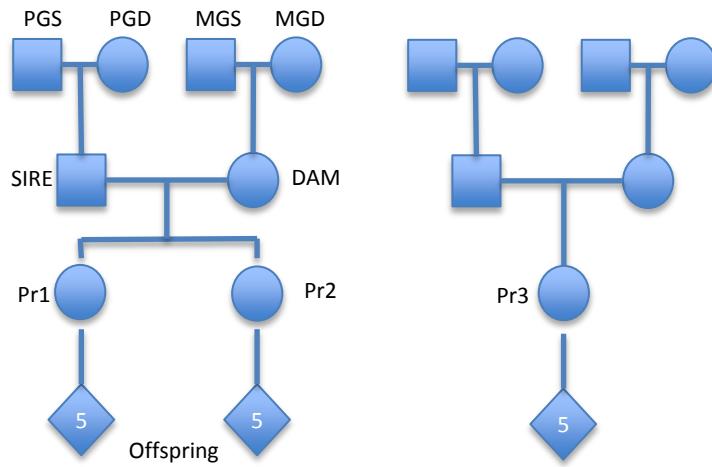




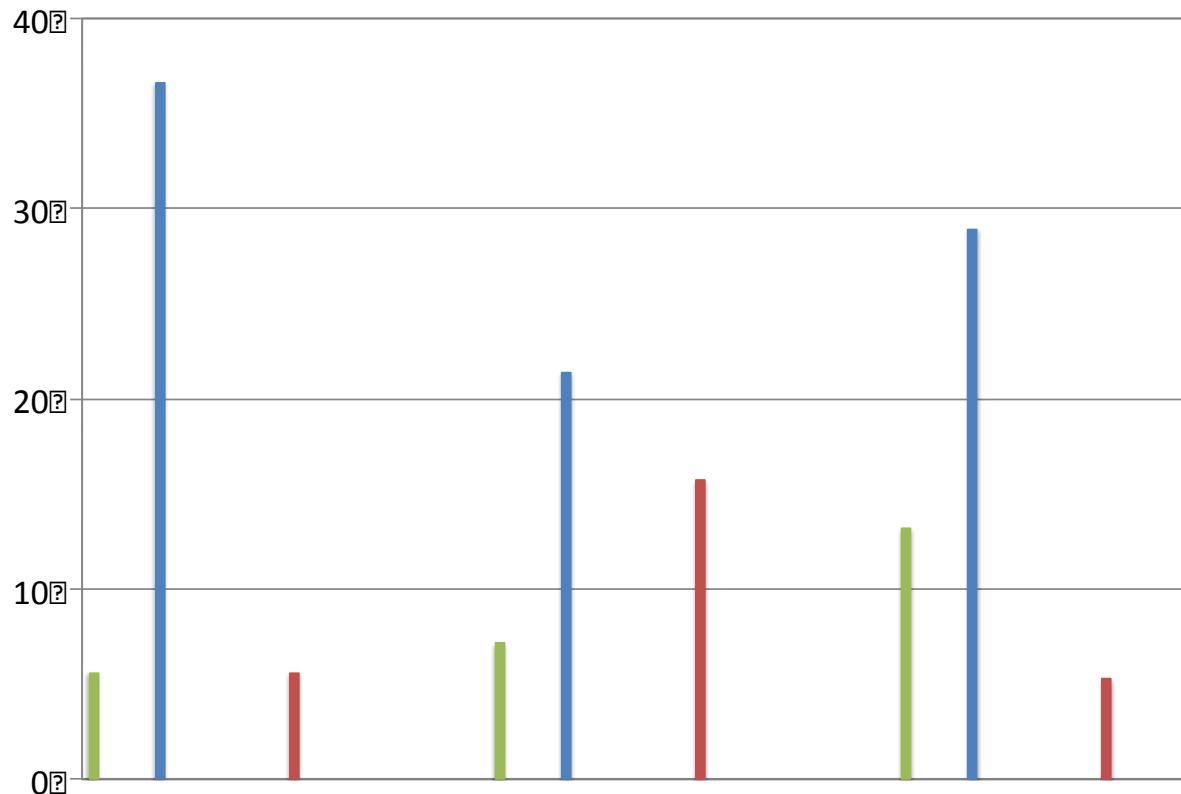
~ 30% of de novo mutations detected
 (standard) *in sperm* are “Pr-M”







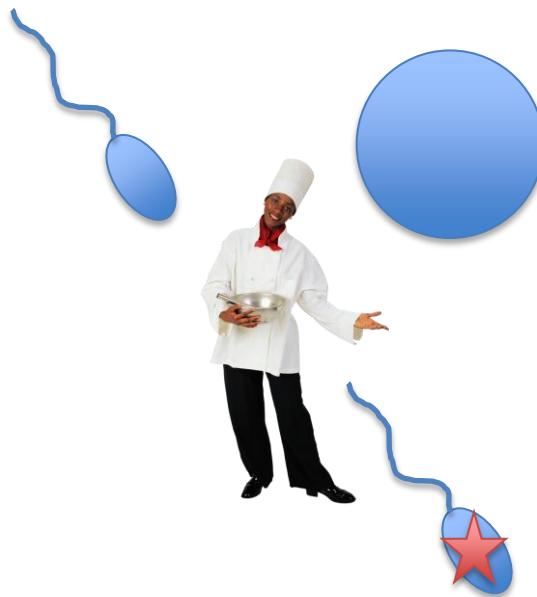
~ 20% of de novo mutations
detected (standard) *in somatic*
DNA (F) are “PR-M” !



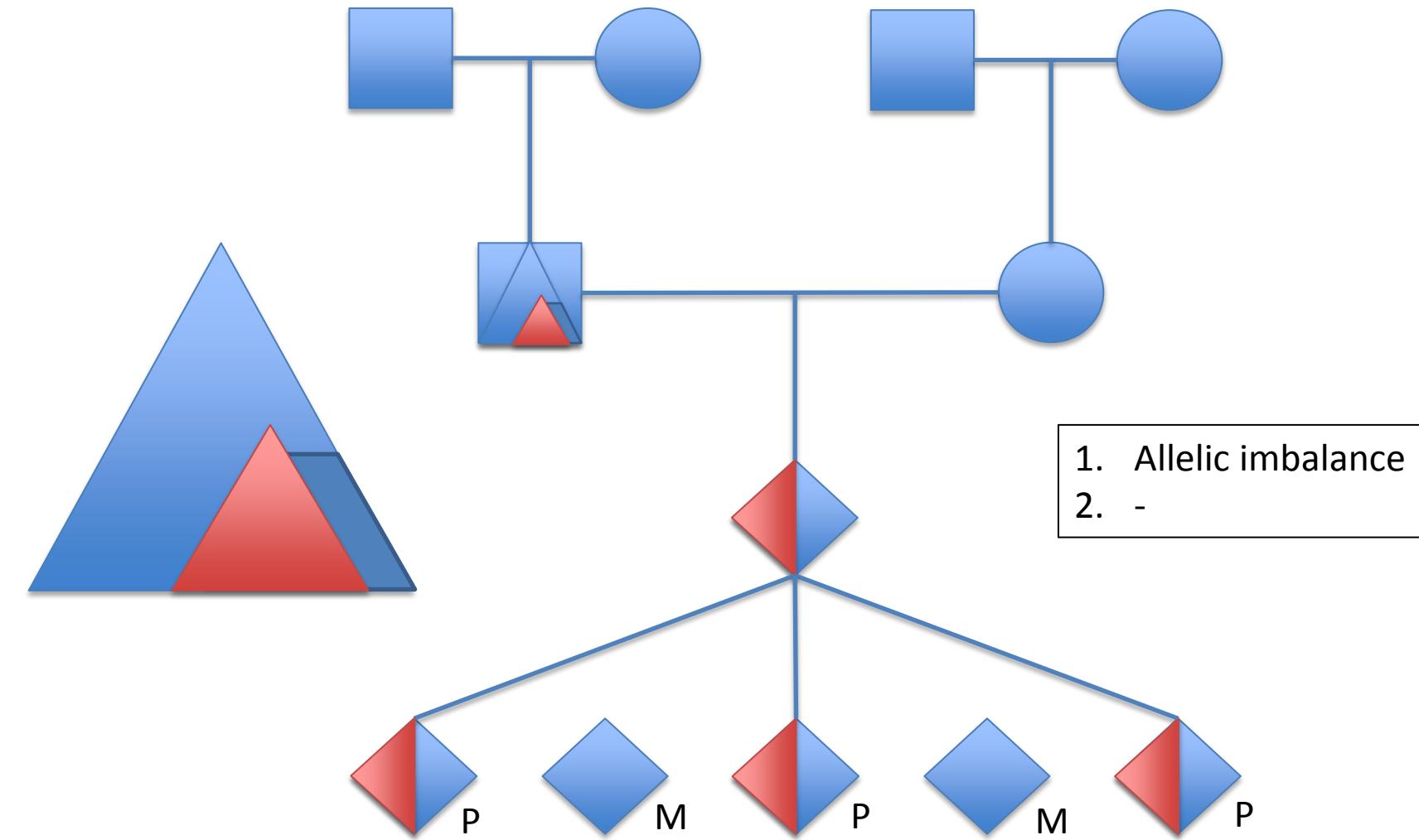
Germ-line de novo mutations

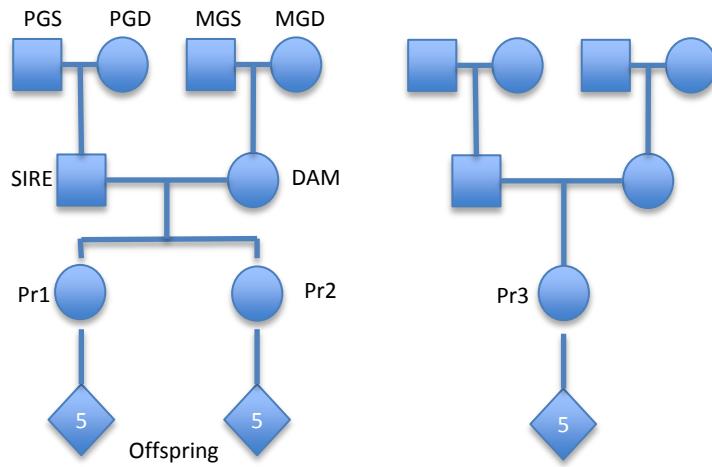
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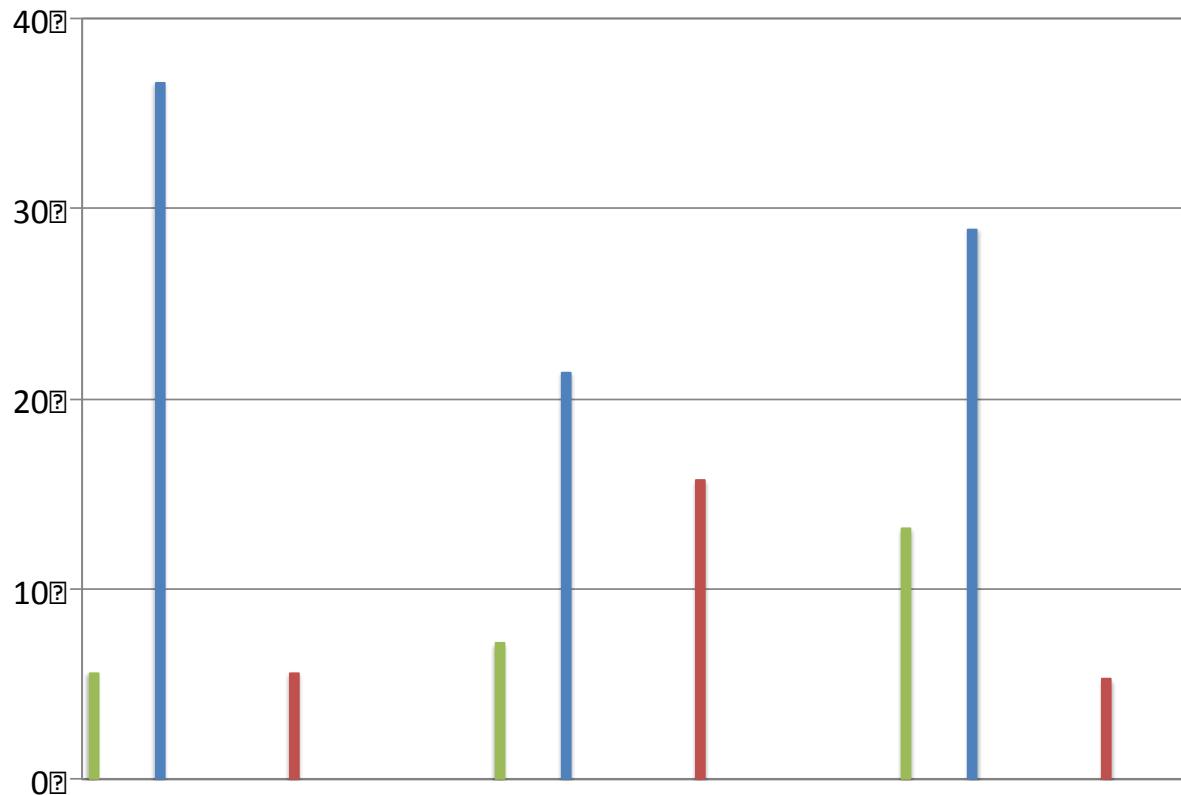


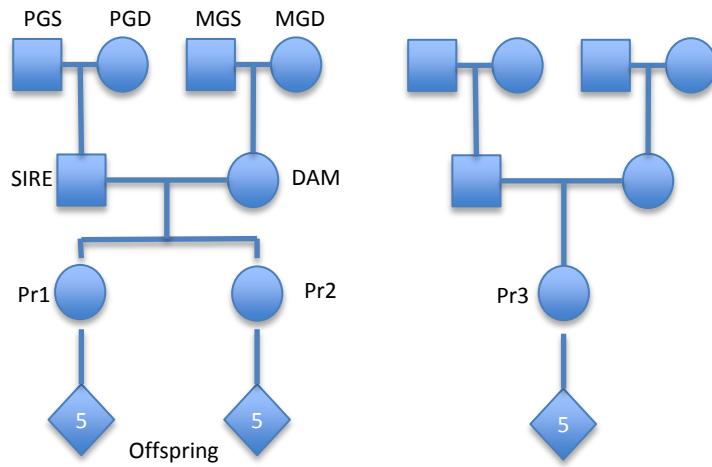
Mosaicism in the parents



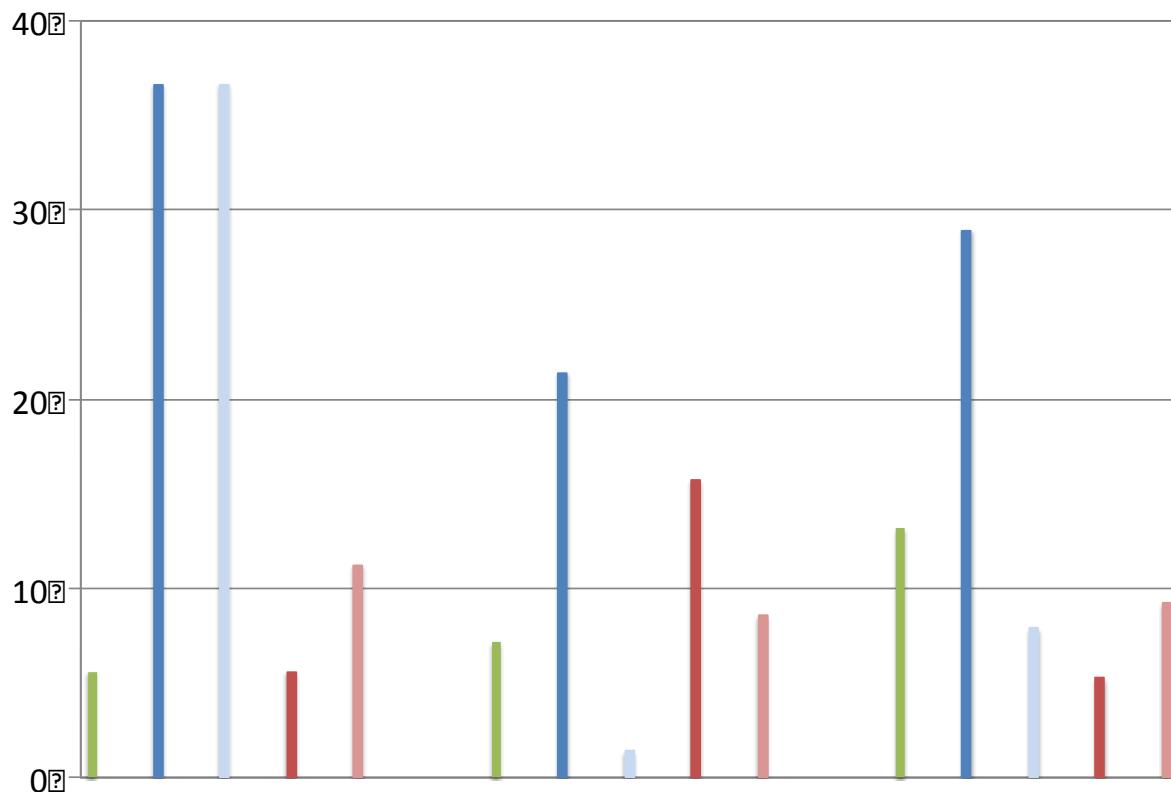


~ 20% of de novo mutations
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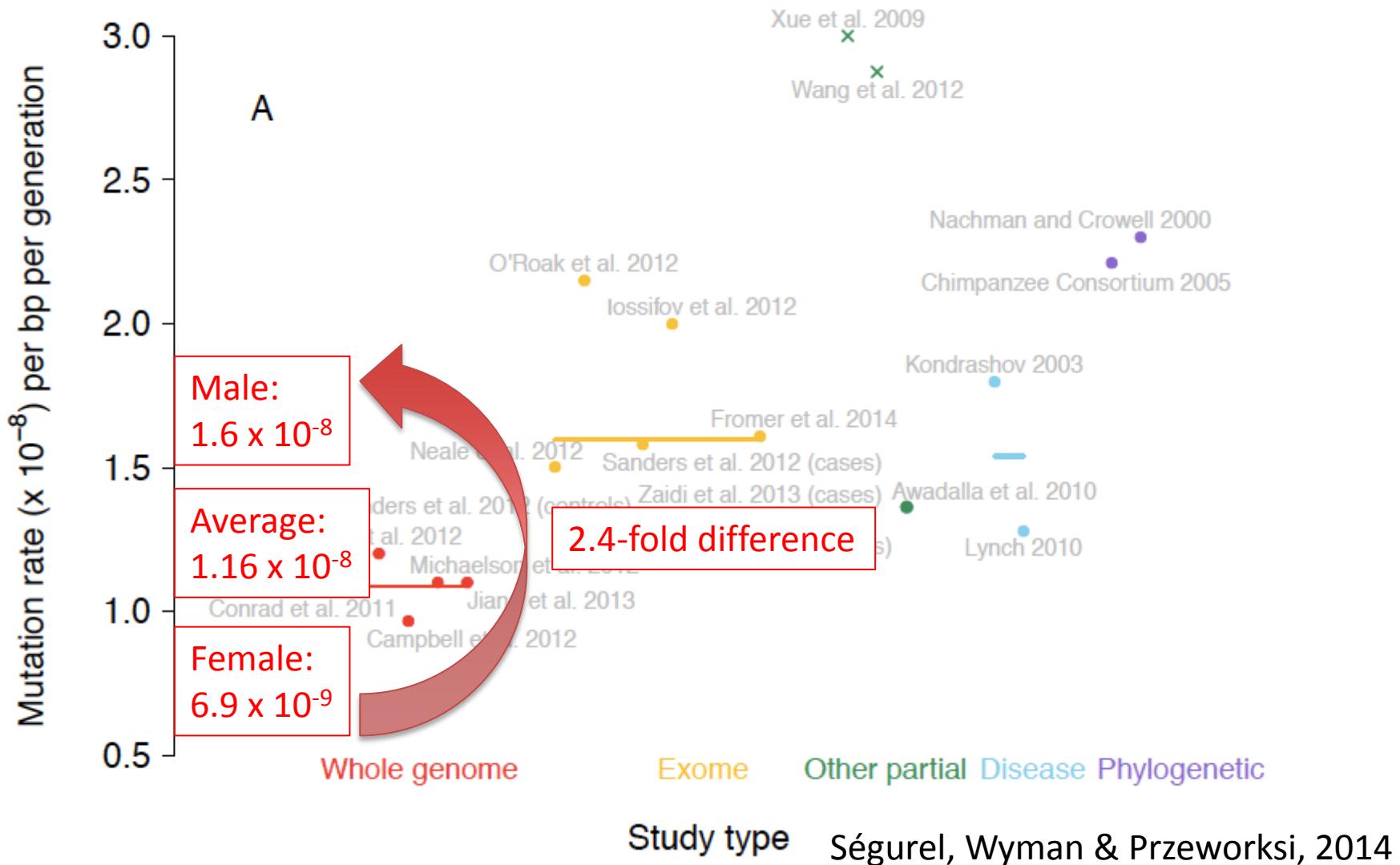


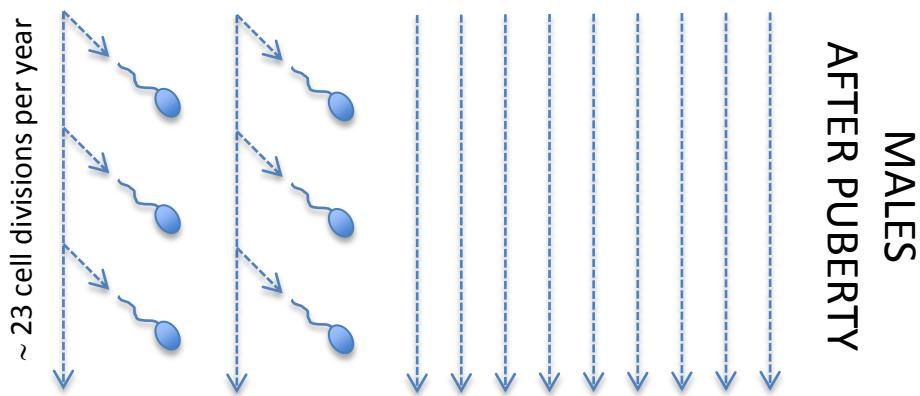
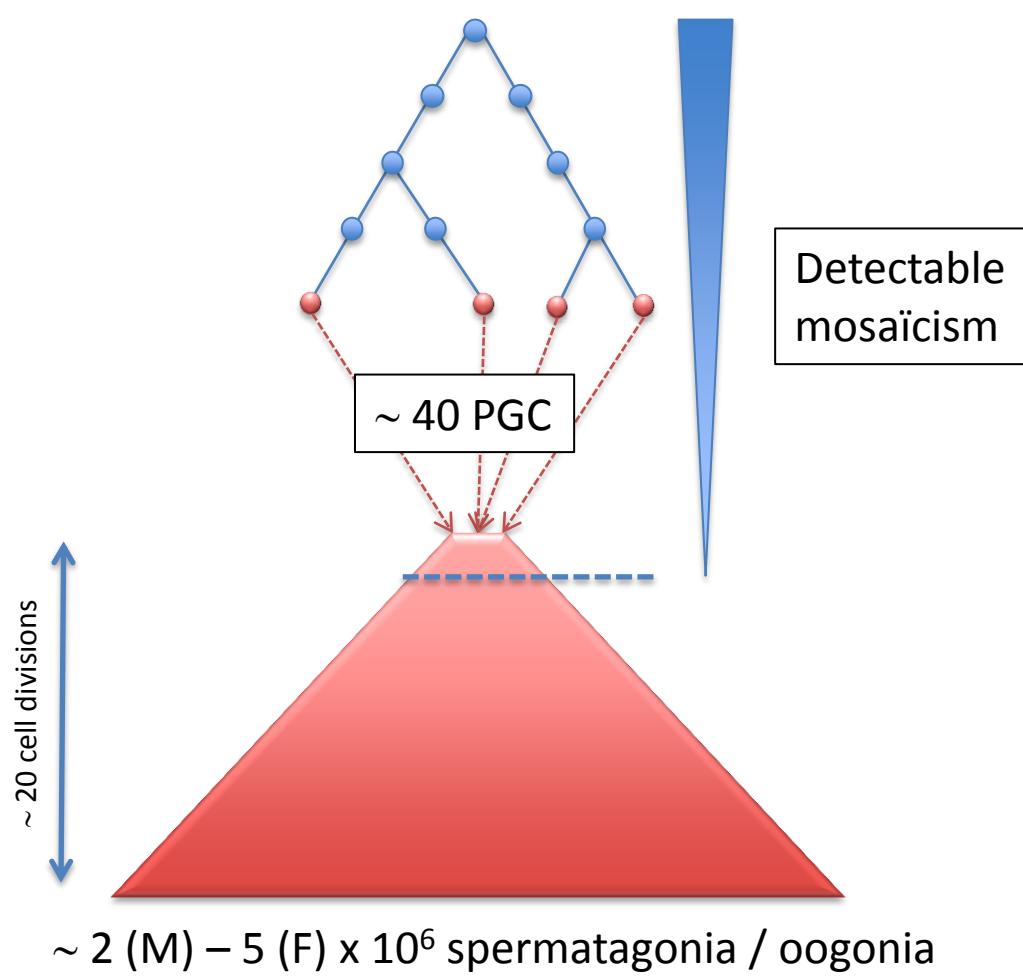
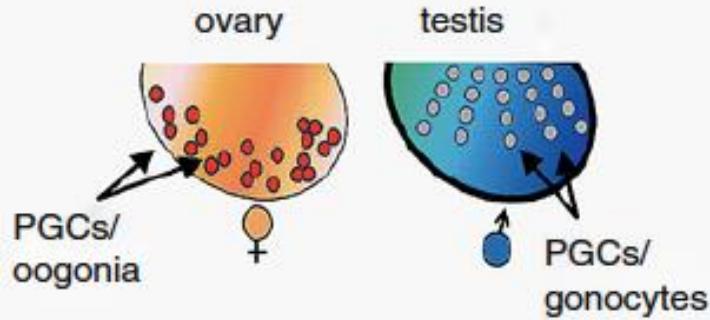
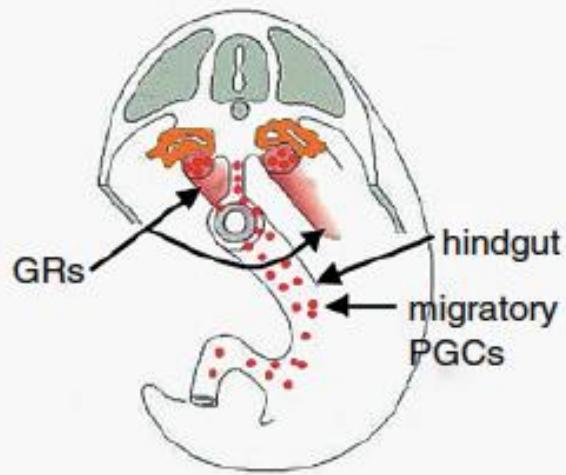
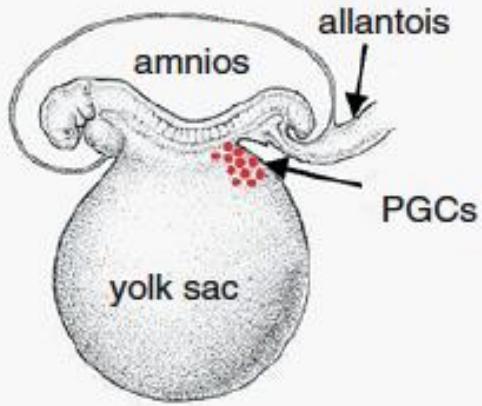


~34% (sperm) & ~52% (oocyte) of
de novo mutations detectable in
parental sperm & somatic DNA !!

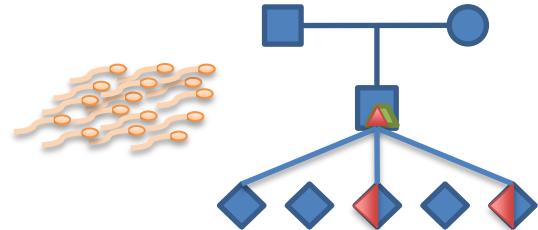
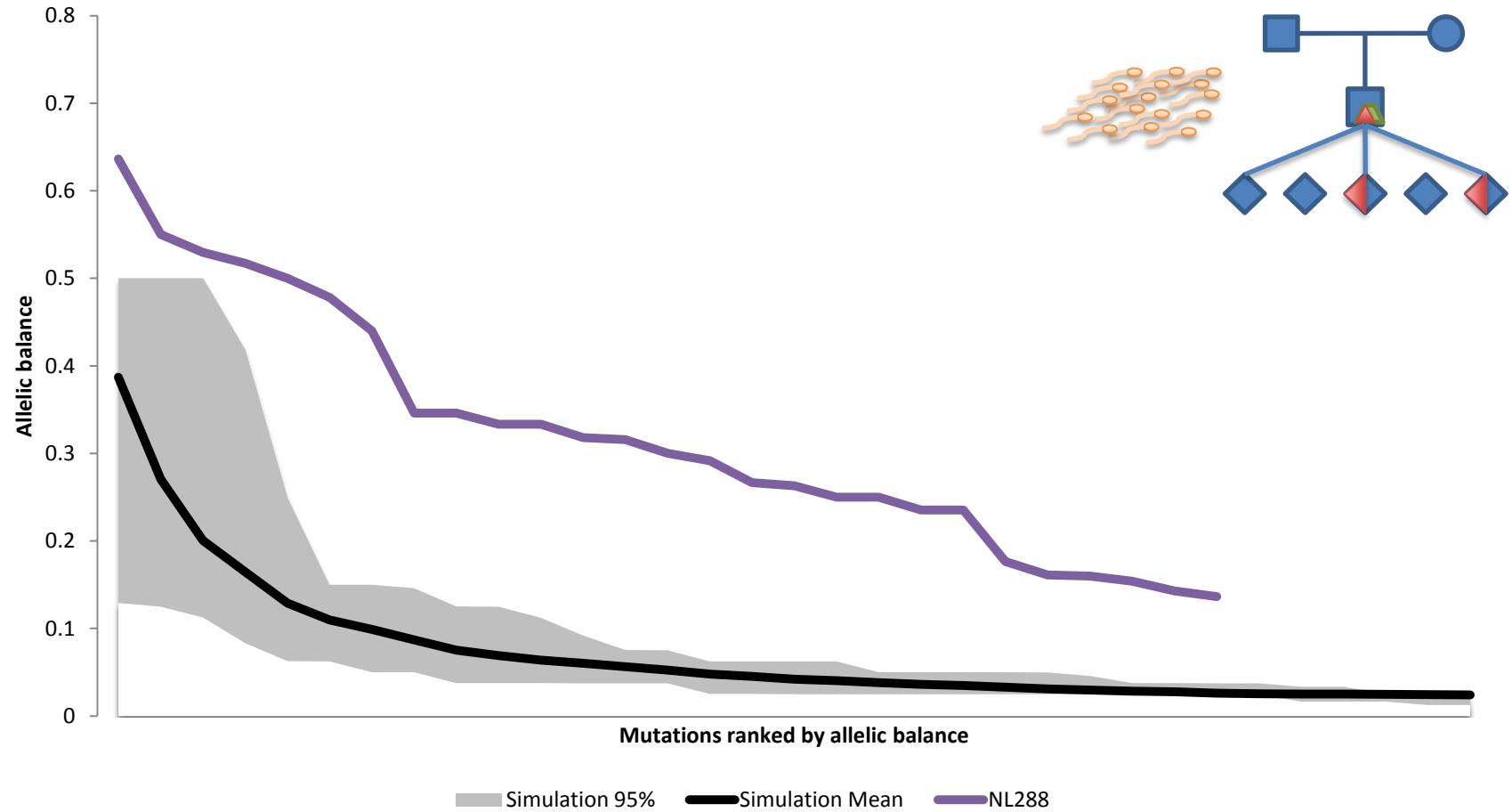


Estimated mutation rate

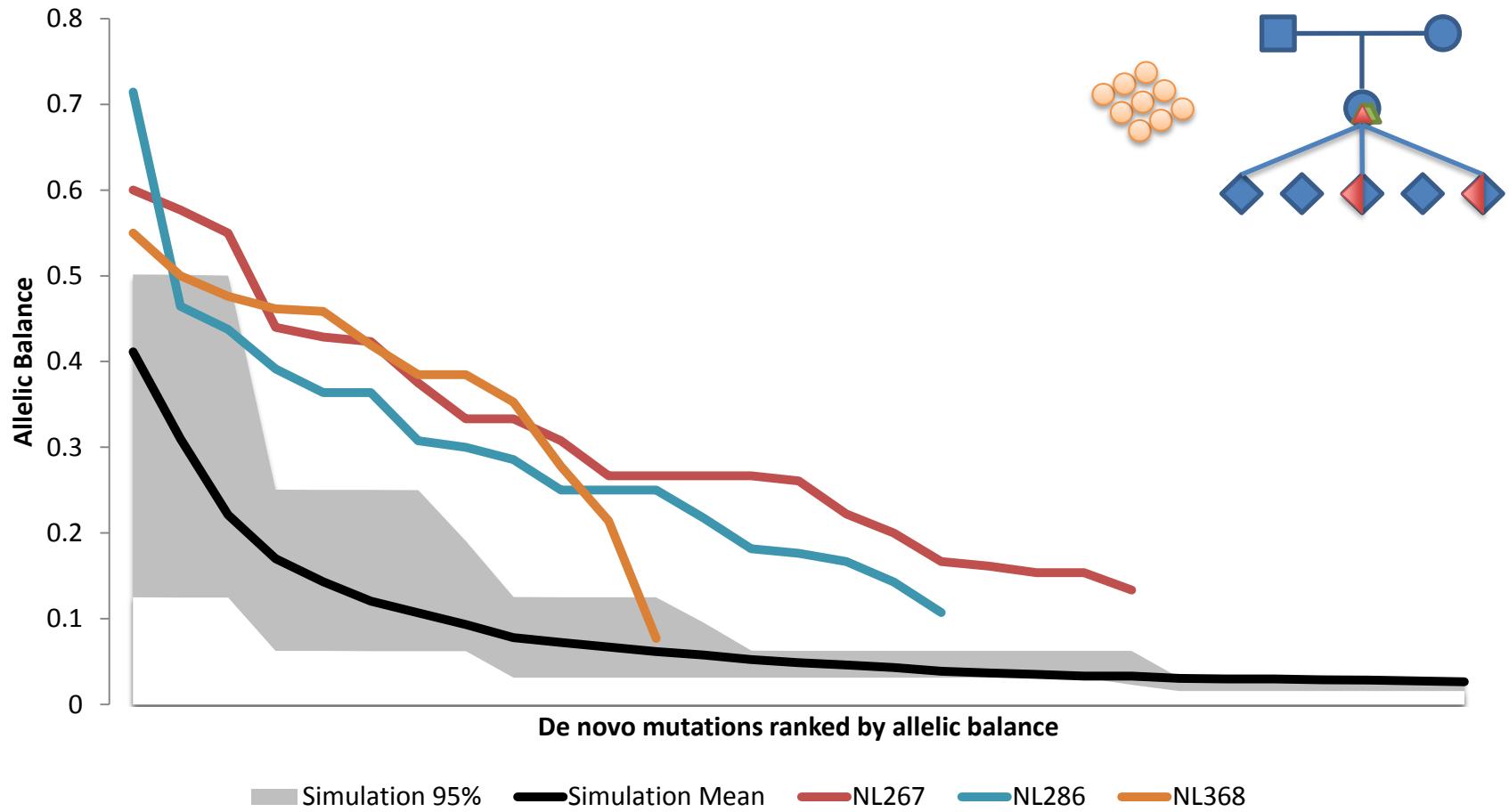




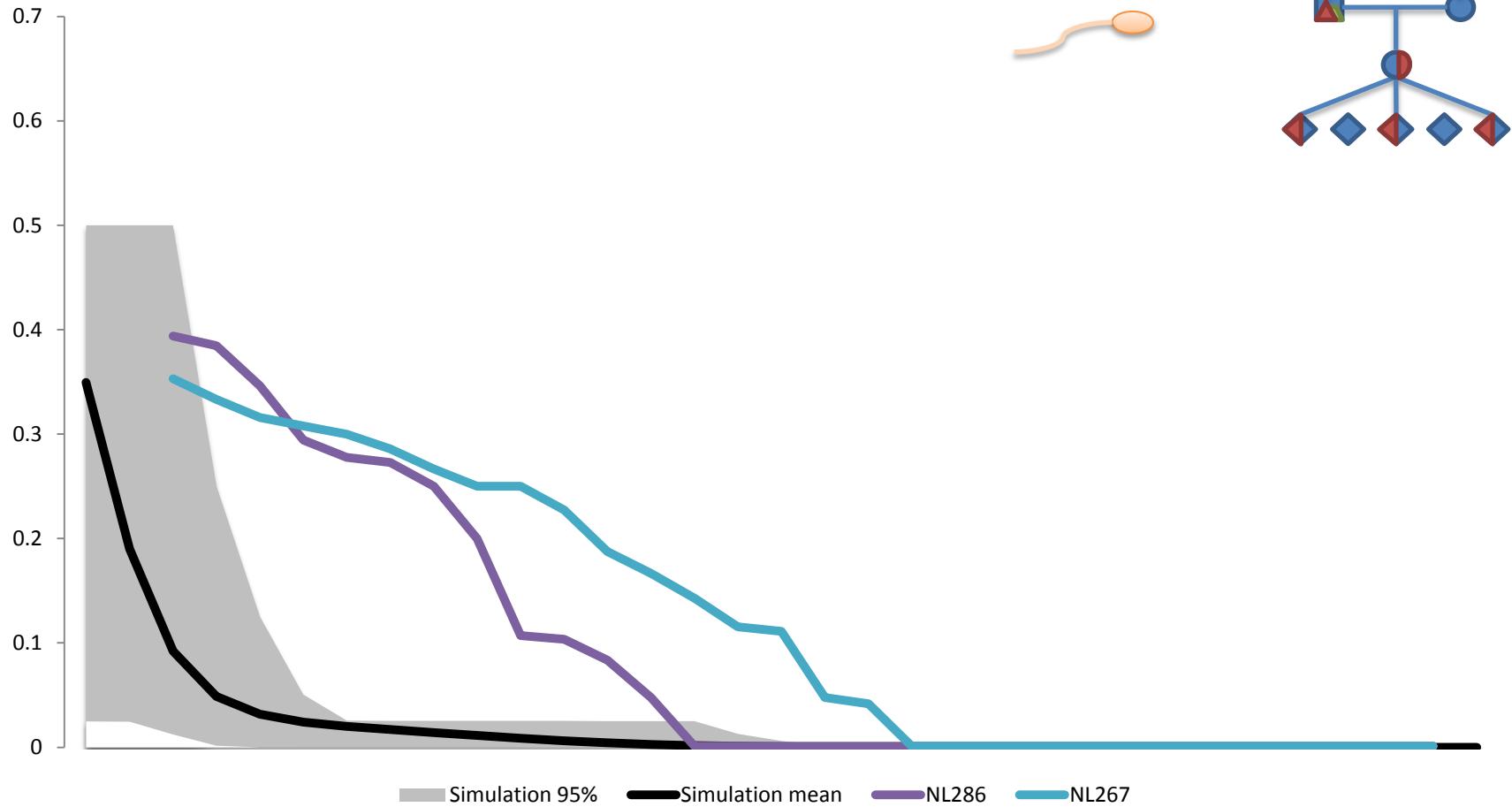
Mosaicism in male proband



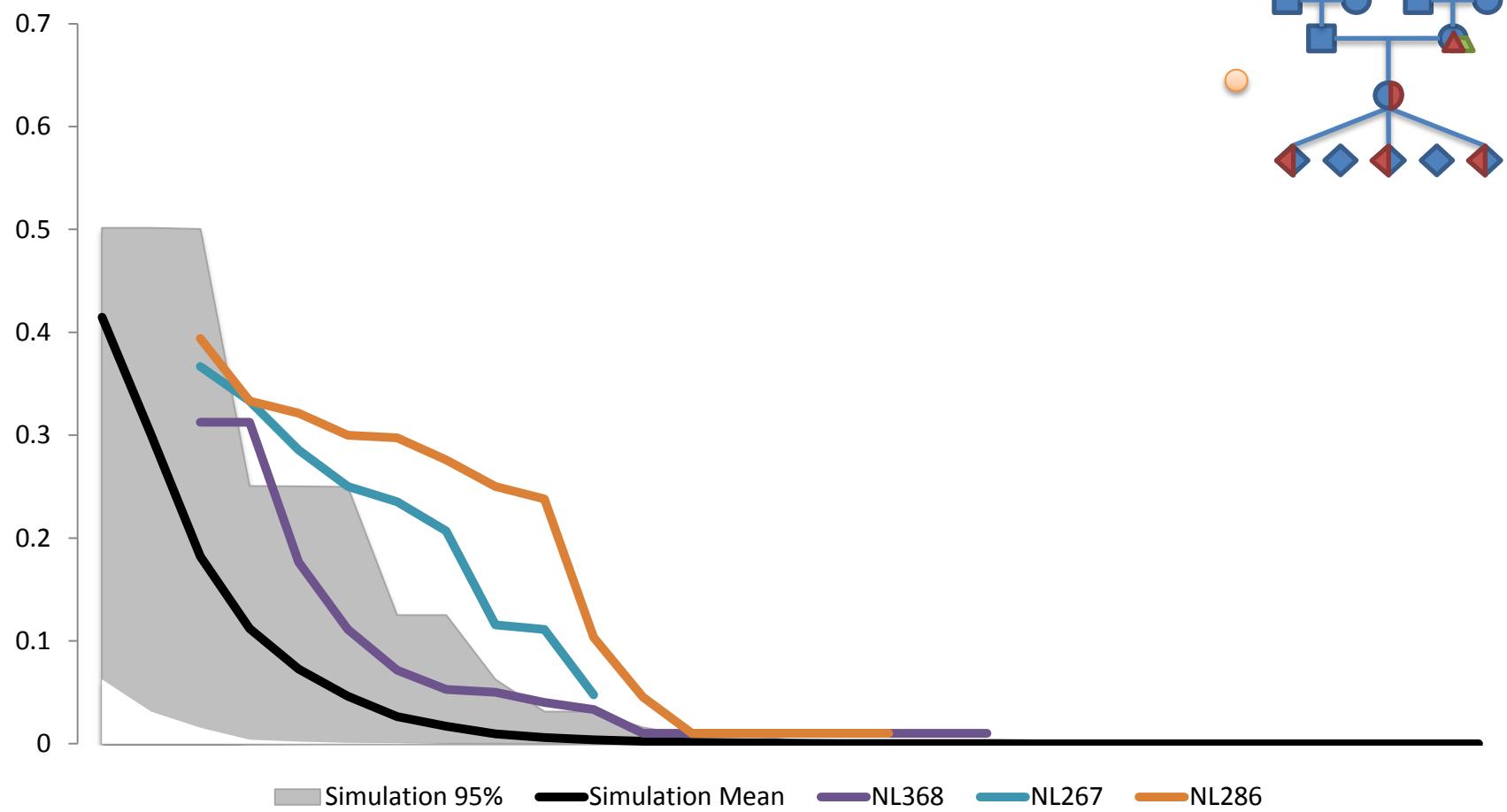
Mosaicism in female probands

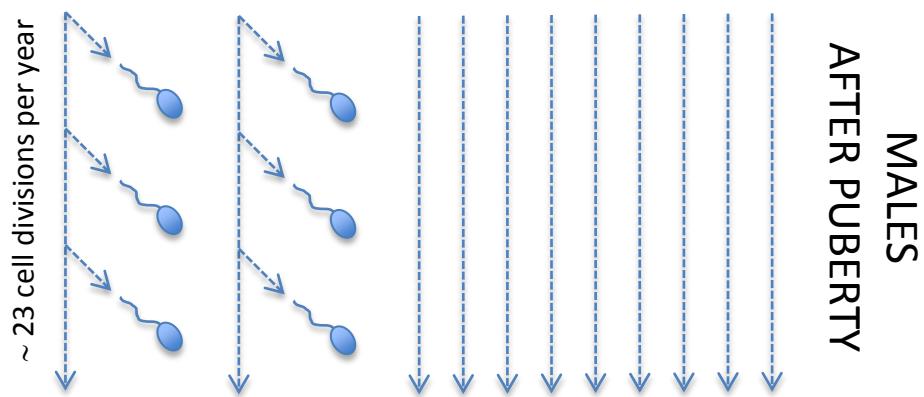
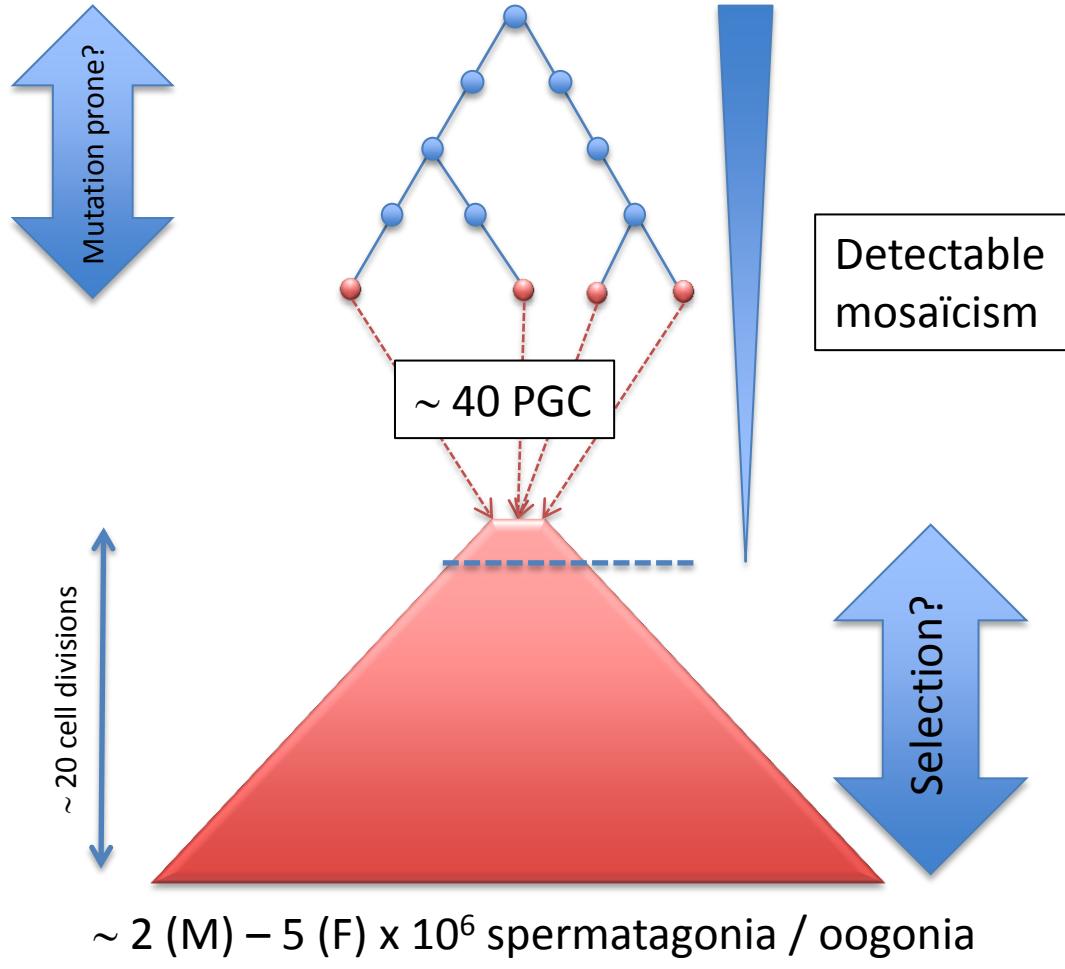
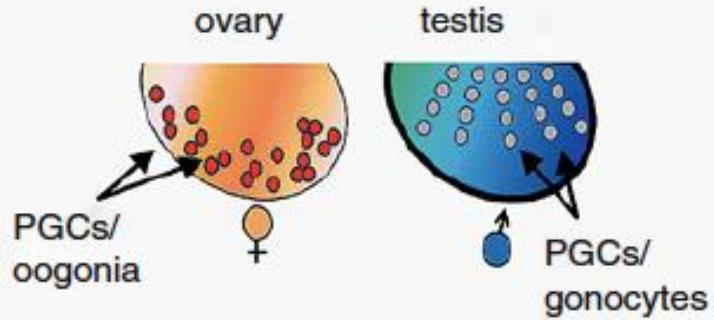
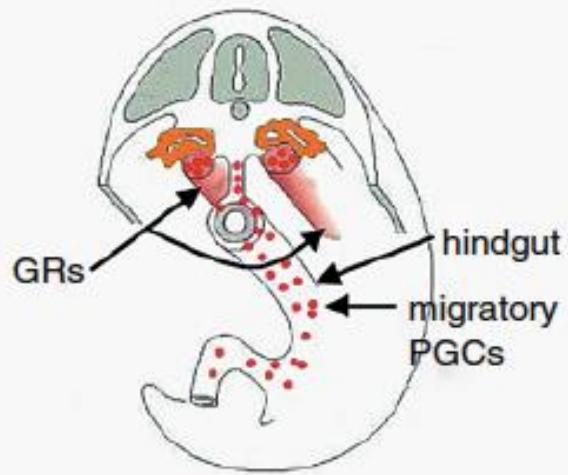
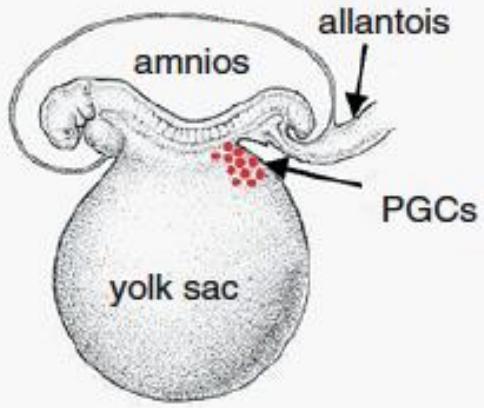


Mosaicism in male parent



Mosaicism in female parents





Conclusions

- Germline and somatic mosaicism of de novo mutations is pervasive ...
- This should be taken into account to accurately estimate mutation rates in the male and female germ-line ...
- It suggests that early cell divisions are particularly prone to mutation events ...

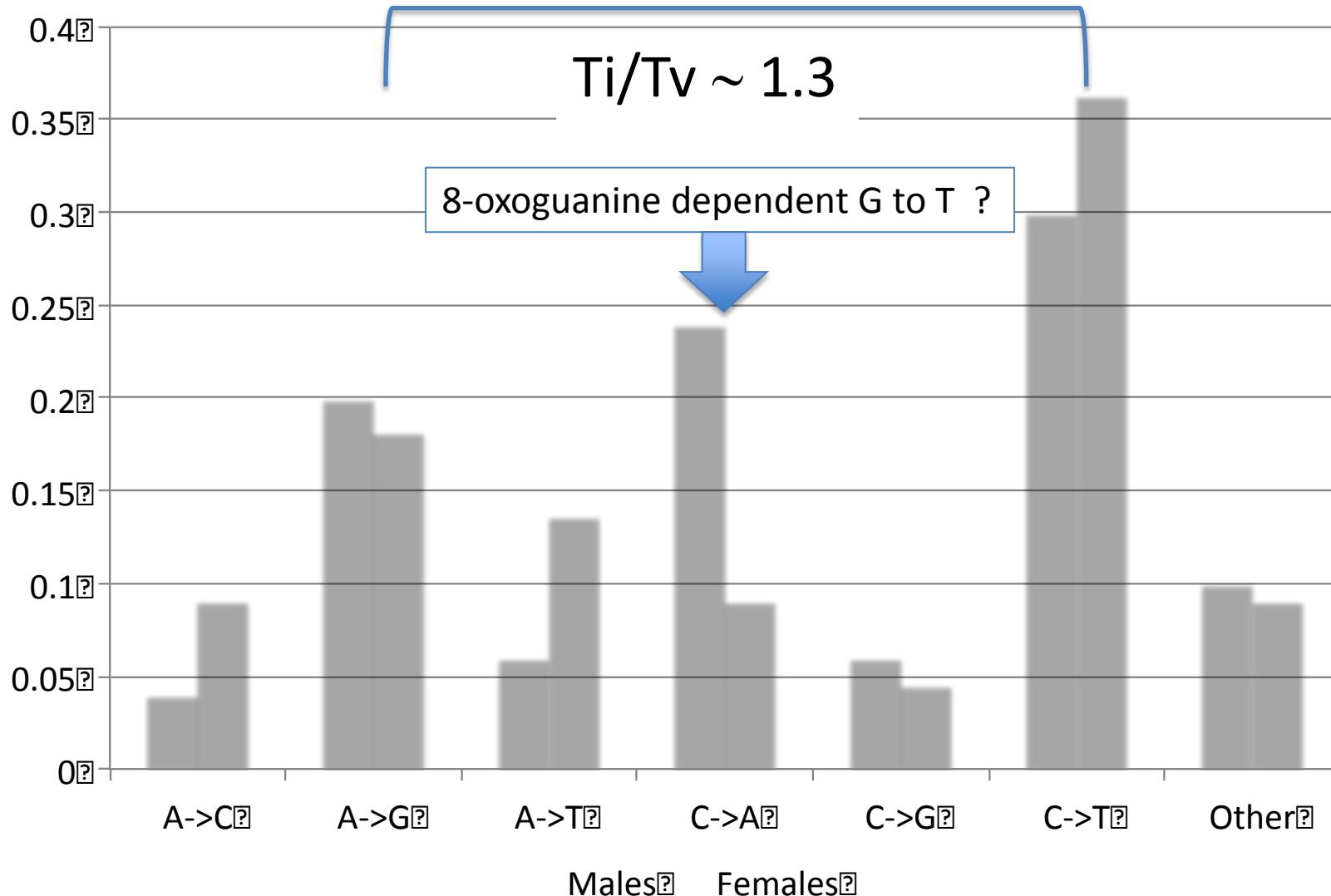
Funding



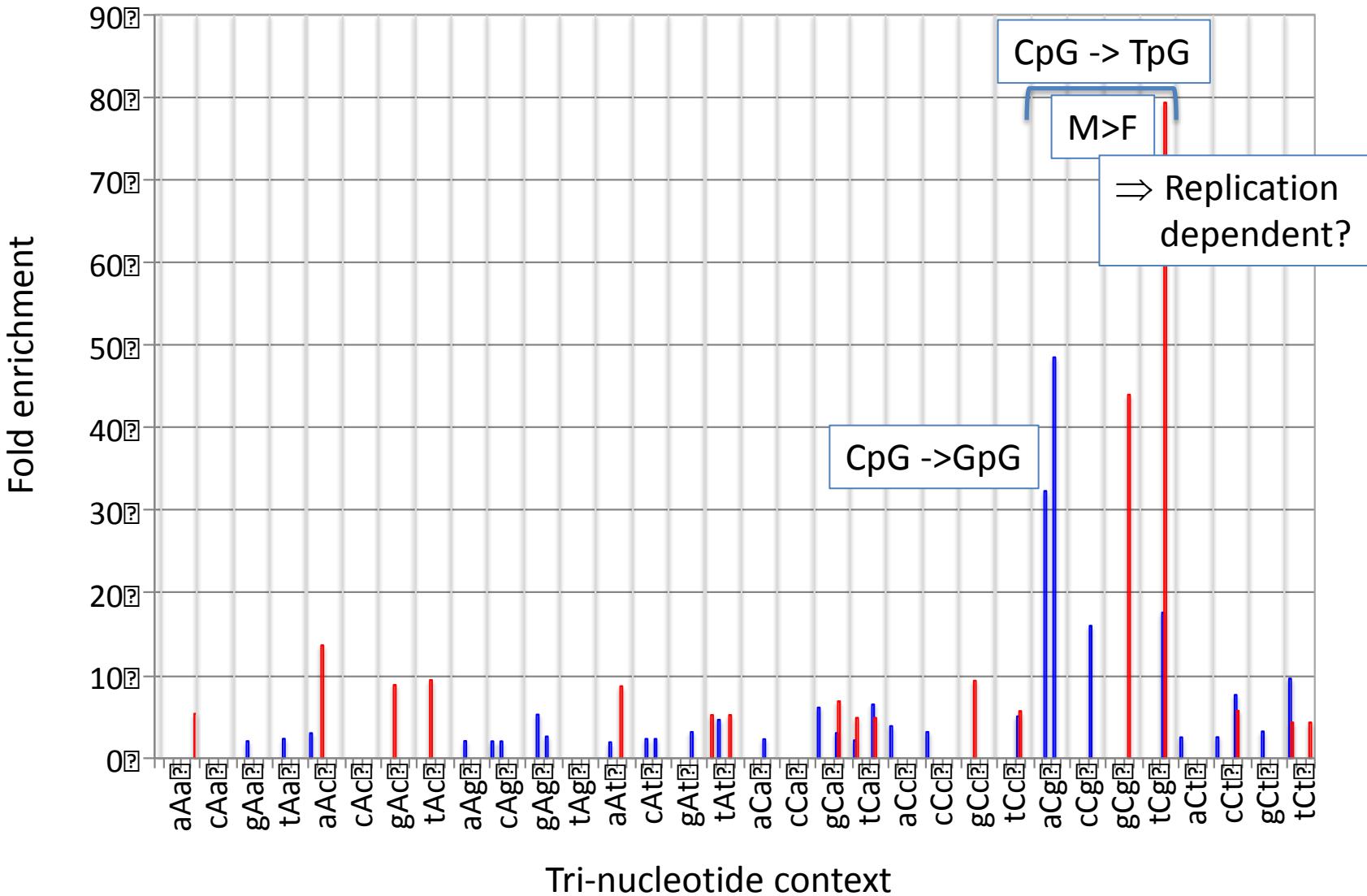
European Research Council



Types of de novo mutations



Types of de novo mutations



Serial translocation via circular intermediates underlies bovine color-sidedness

Michel Georges
University of Liège
Belgium

Colorsidedness, lineback or witrik => dominant *Cs* allele



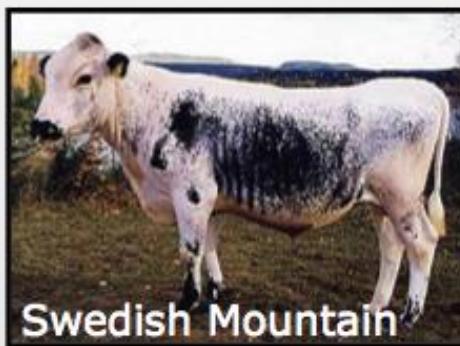
Belgium
Blue



Witrick



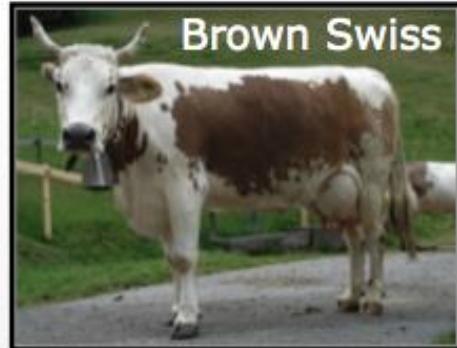
Irish
Moiled



Swedish Mountain



Fogera



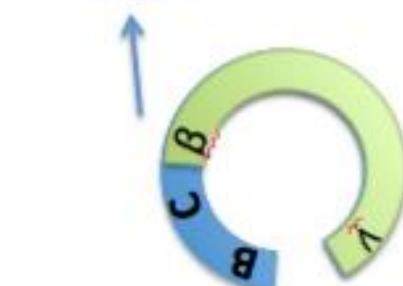
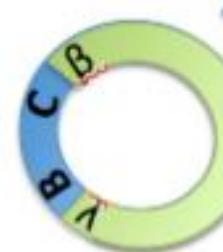
Brown Swiss



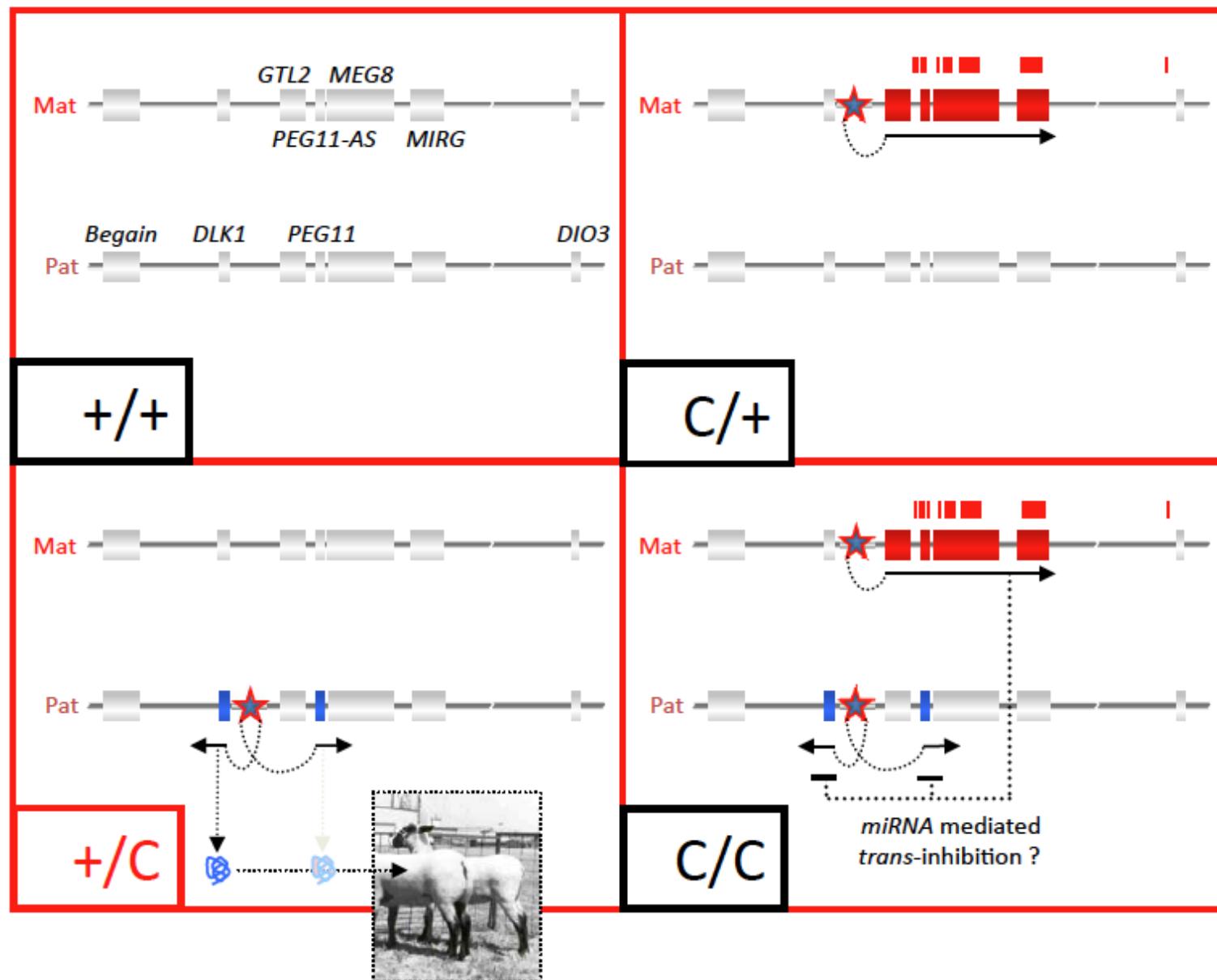
Pinzgauer



Vosgienne

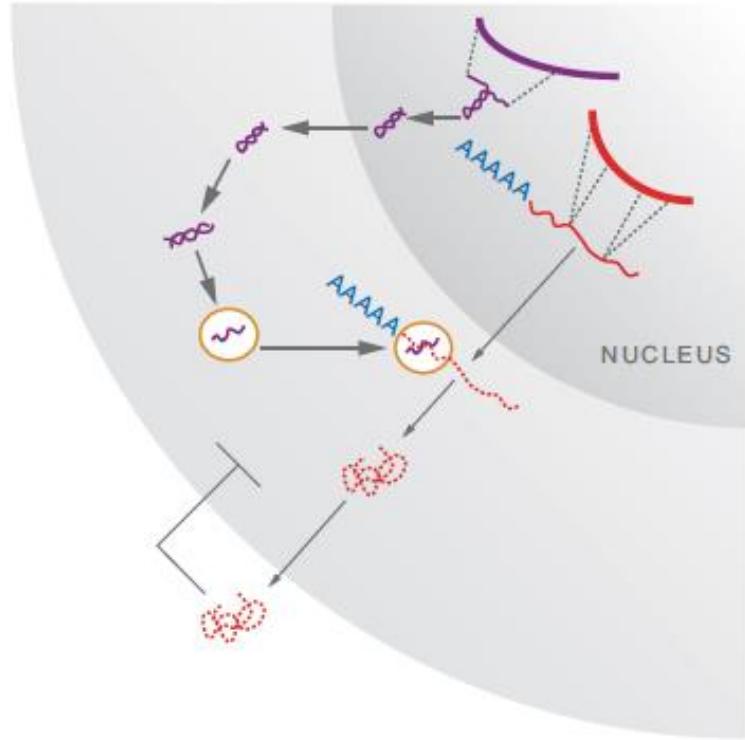
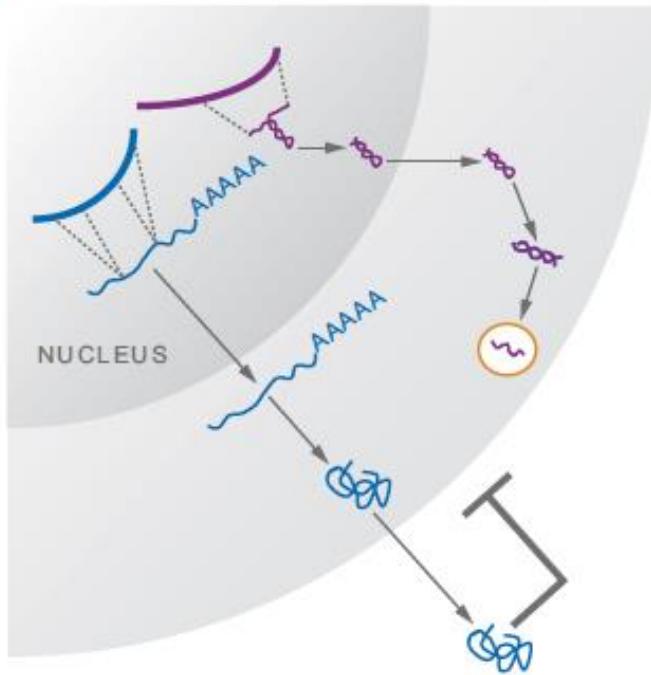


Polar overdominance at the calipyge locus



Texel Sheep

(c)



Wild-type sheep



Texel sheep