Mutations in animals and plants: an introduction

Ron and Joyce Bond
(UK's (World's?) oldest living married couple)

« The Major Oak », Sherwood Forest, Nottinghamshire, England (800-1,000 years old, UK's most visited tree)

Thibault Leroy

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https://thibaultleroyfr.github.io

Cautionary statements

This course is just an introduction and we will only cover:

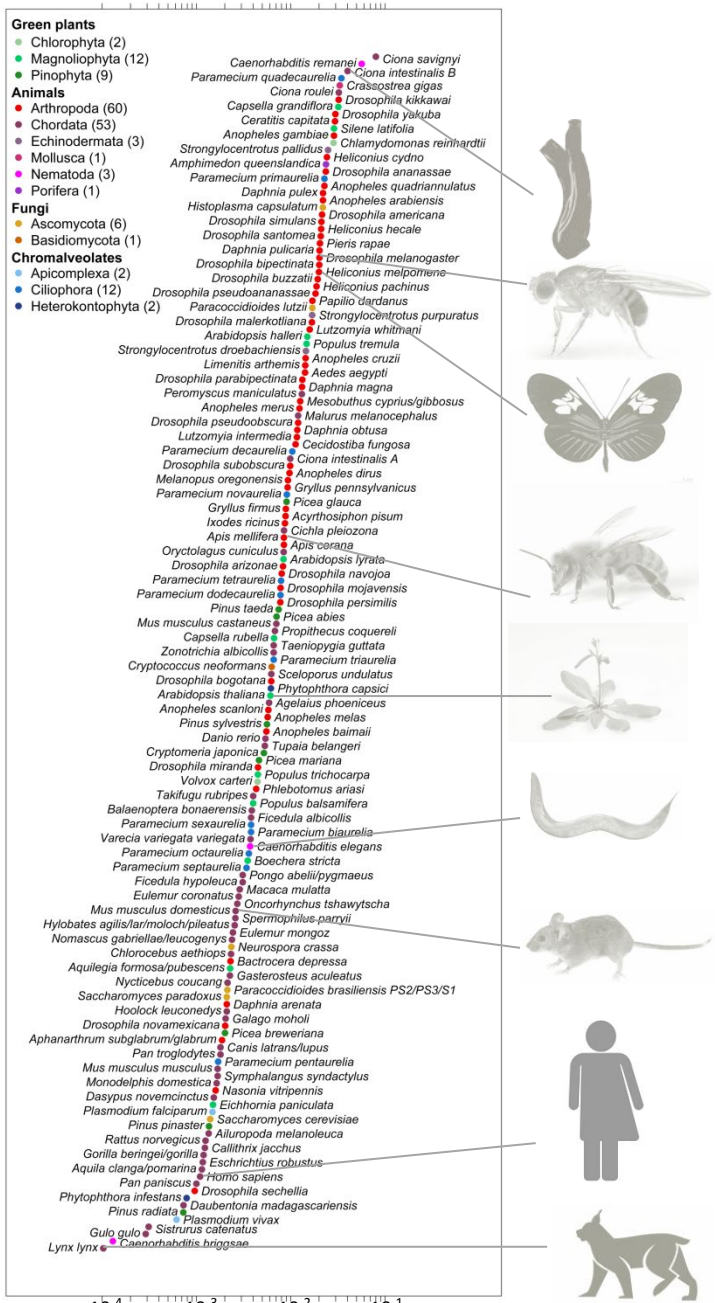
- Alteration in the DNA sequence (no epigenetics/epigenomics)
- Simple de novo mutations (DNMs) generating single nucleotide polymorphisms (SNPs; *i.e.* no copy number variations, indels, interchromosomal inversion or translocation, …)
- Animal & plant species

Why mutation rate (μ) is a so important parameter in biology?

Estimating the levels of genetic diversity across the tree of life

1:AAATACCAACAAC | 1 difference
2:AAATACCATCAAC | 1 difference
3:AAATACCATCAAG
4:AAATACCATCAAC …
5:AAATACCATCGAC

π *the average number of nucleotide differences per site between pairs of sequences*



Leffler et al. Plos Biol 2012

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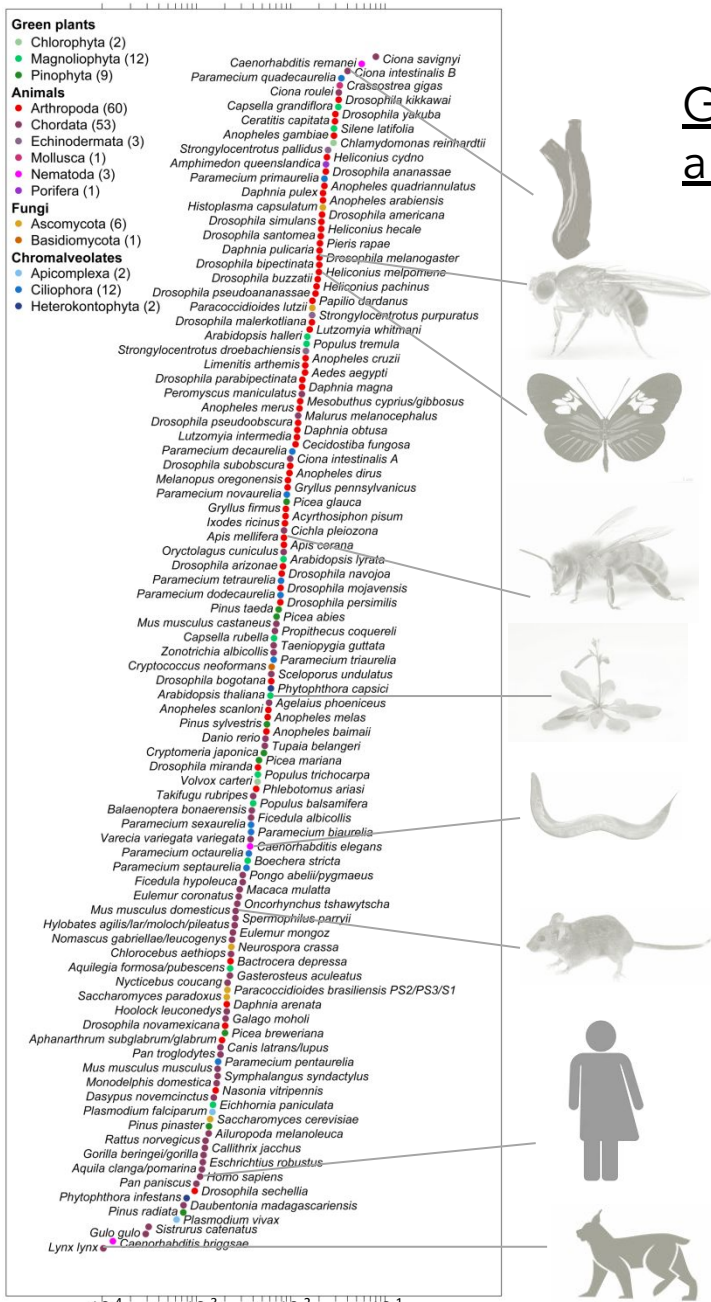

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Genetic diversity within a population

(Standing genetic variation)

At mutation-drift equilibrium:

$\pi = 2 * c * Ne * \mu$

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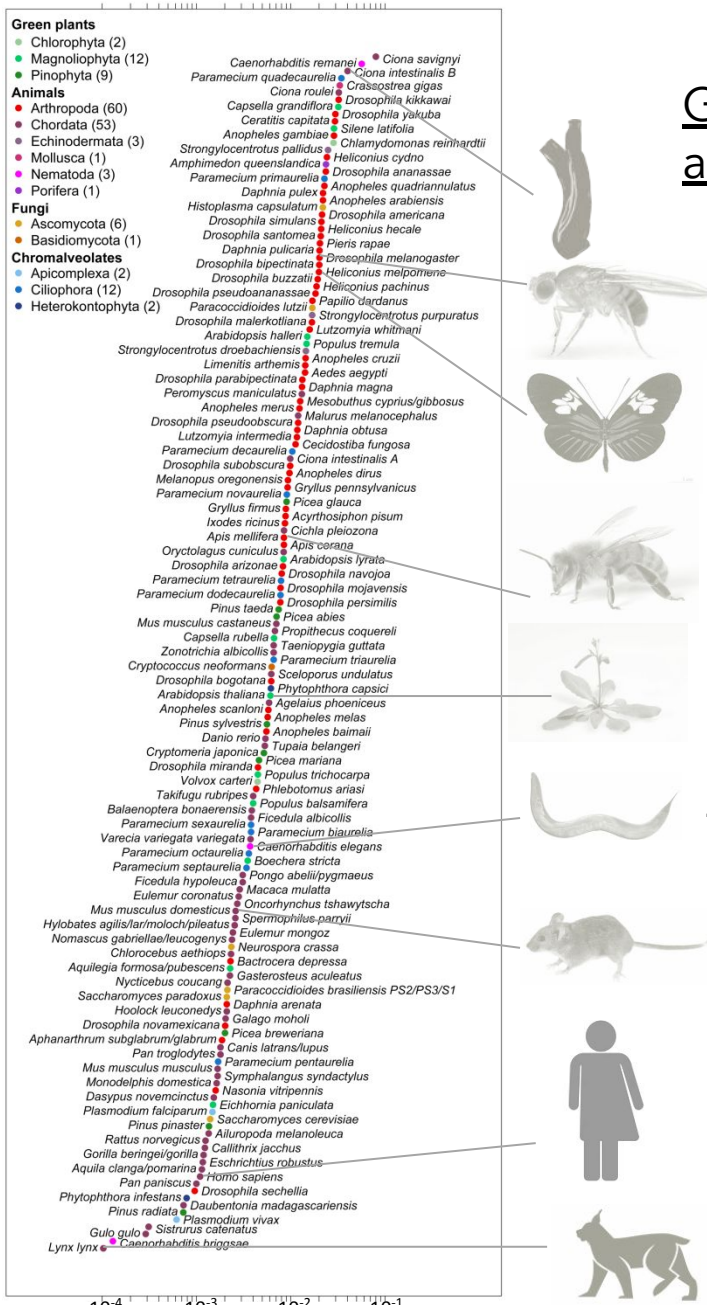

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Genetic diversity within a population

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At mutation-drift equilibrium:

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Divergence between species

Following the neutral theory:

Rate of neutral substitutions = $2\,Ne * \mu * \frac{1}{2\,Ne} = \mu$

Molecular clock (Kimura, 1968)

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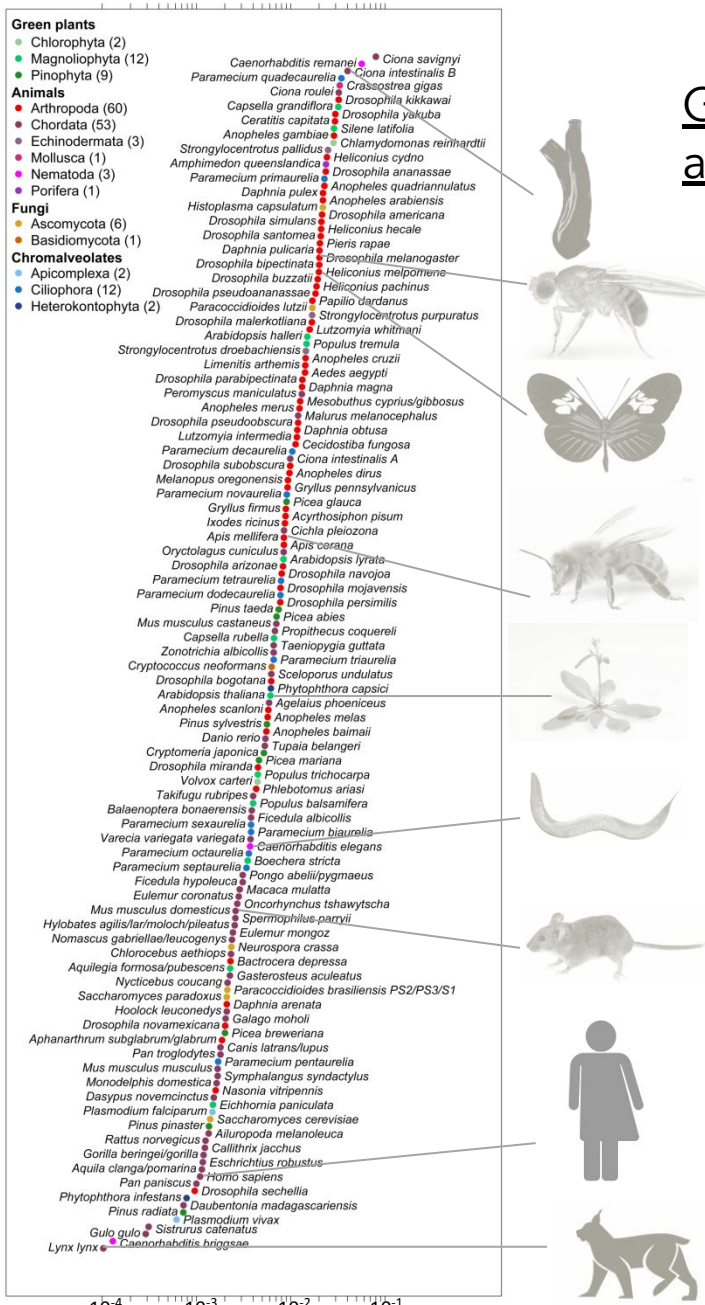
Estimates of heritable mutation rates are crucial for interpreting patterns of broad scale biodiversity, from patterns of diversity within species to divergence among species.



Leffler et al. Plos Biol 2012

Genetic diversity within a population

(Standing genetic variation)

At mutation-drift equilibrium:

$\pi = 2 * c * Ne * \mu$

Divergence between species

Following the neutral theory:

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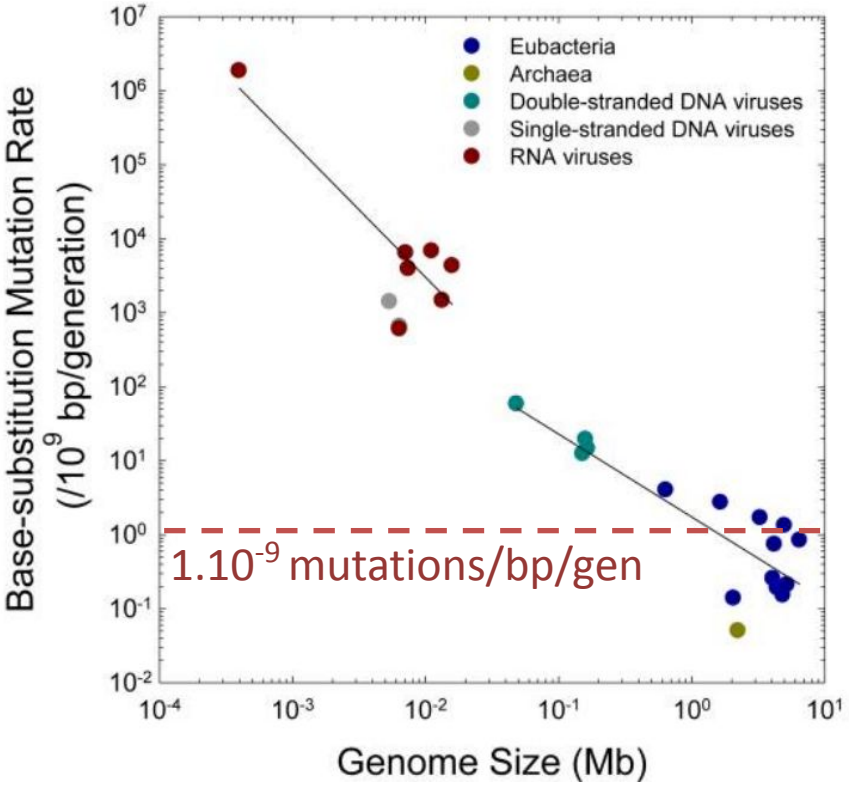
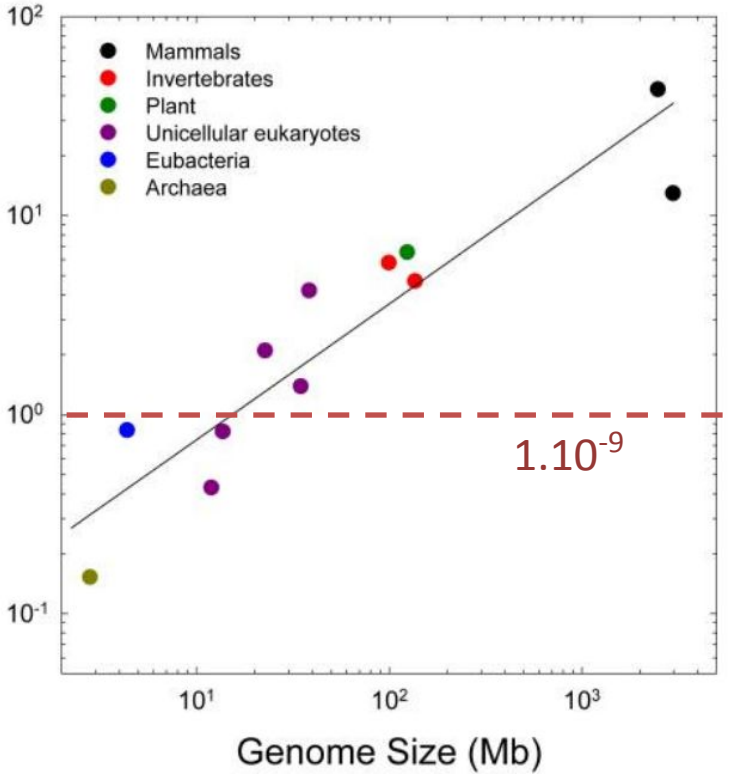
Molecular clock (Kimura, 1968)

Mutation rate (μ) is variable among species

Viruses & bacteria



(Bacteria &) Eukaryotes

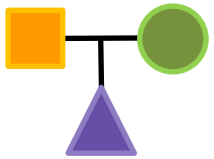


Lynch, 2010 Trends Genet

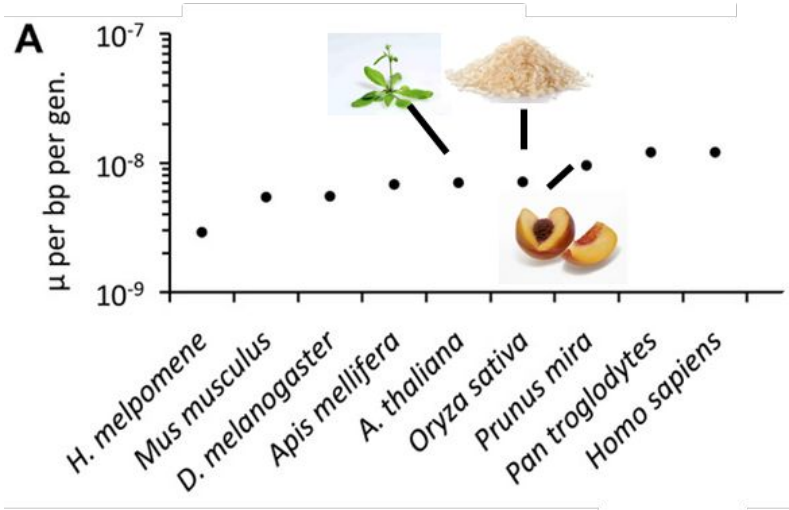
Mutation varies depending across the tree of life, spanning several order of magnitude!

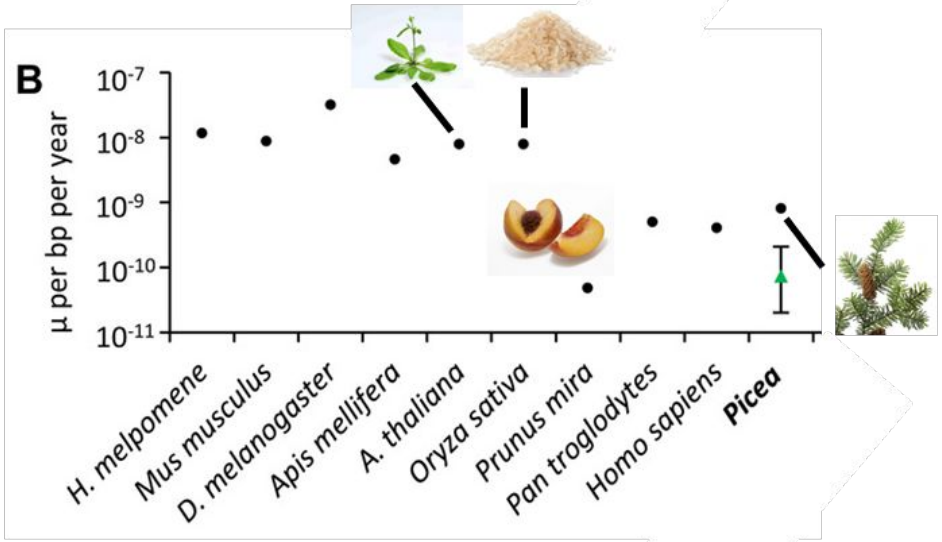
Mutation rate (μ) is variable among species

Trio sequencing:



Number of de novo mutations (DNM) passed to the progeny





Mutation—The Engine of Evolution: Studying Mutation and Its Role in the Evolution of Bacteria

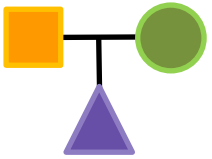
Ruth Hershberg

"[…] we **do not know nearly enough about mutation** and that recently several of our decades-old assumptions were shown to be mistaken, in light of newly available data."

Modified from Hanlon *et al.* 2019 Evolution Letters

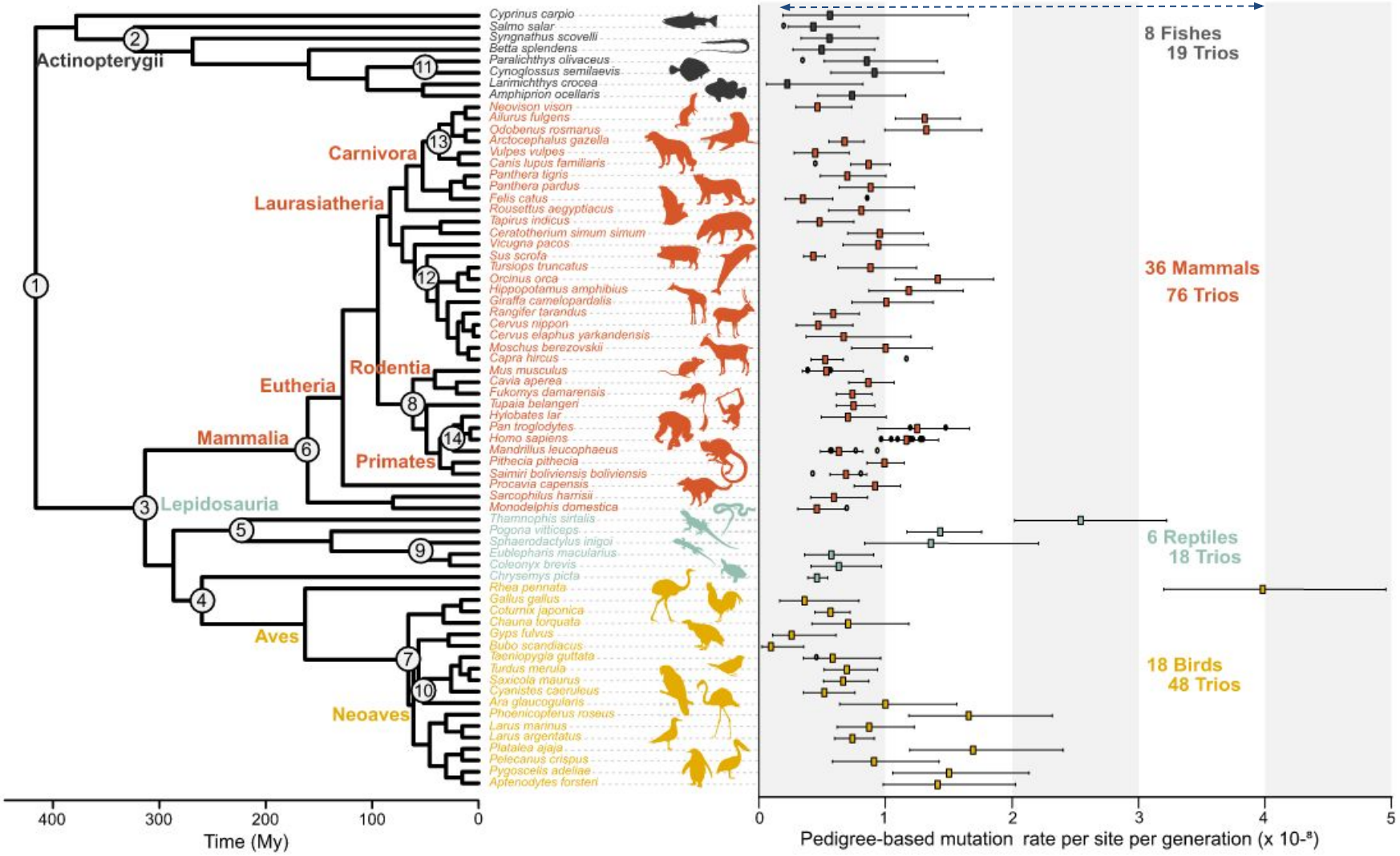
Mutation rate (μ) is variable among species

Trio sequencing:



Number of de novo mutations (DNM) passed to the progeny

40-fold difference!

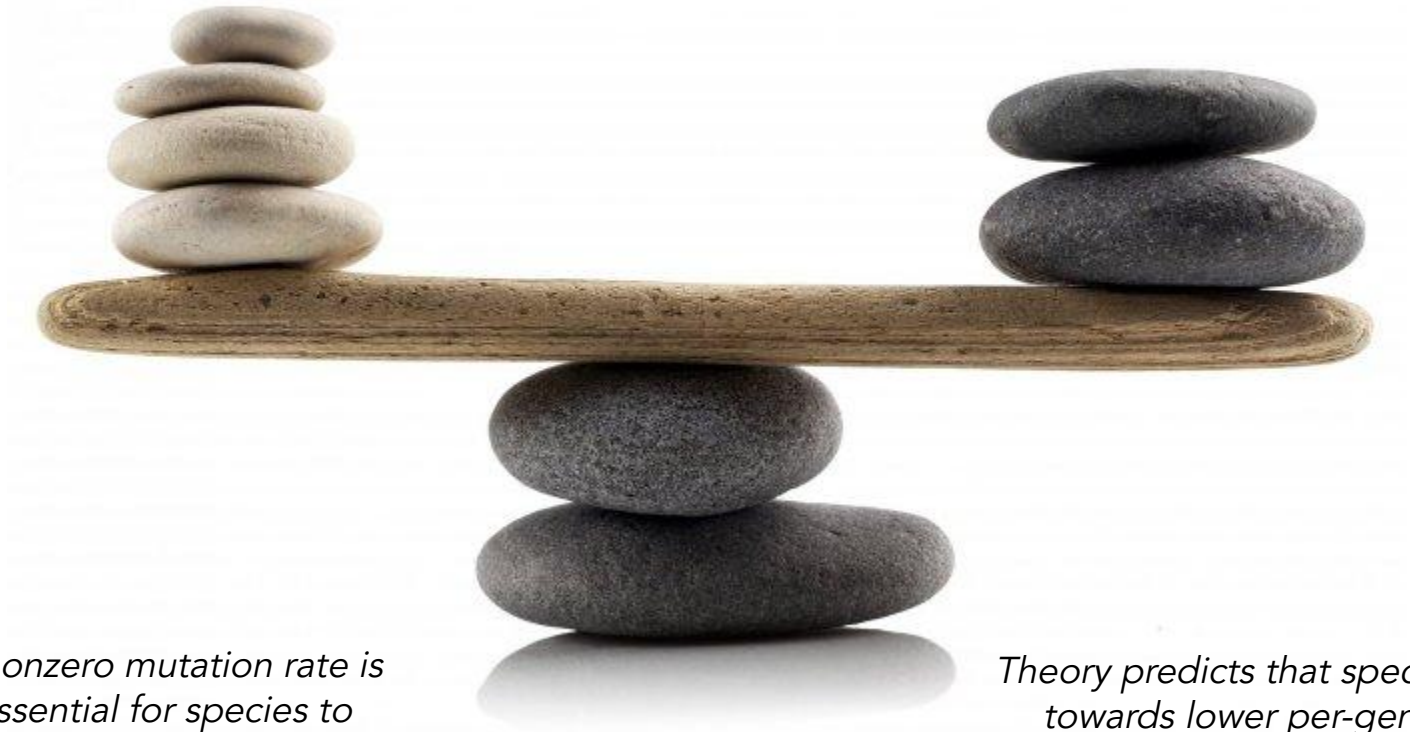


Bergeron *et al.* 2023 Nature

Why do mutation rates vary among species?

Evolvability
(some new adaptive mutations)

Mutational burden
(Deleterious mutations)



A nonzero mutation rate is essential for species to continuously adapt to environmental changes and perturbations

Theory predicts that species evolve towards lower per-generation mutation rates to avoid the accumulation of an increasing burden of deleterious variants (e.g. Kondrashov et al. 1988 Nature)

Heritable and non-heritable mutation detection in animals and plants

Ron and Joyce Bond
(UK's (World's?) oldest living married couple)

?

« The Major Oak », Sherwood Forest, Nottinghamshire, England (800-1,000 years old, UK's most visited tree)

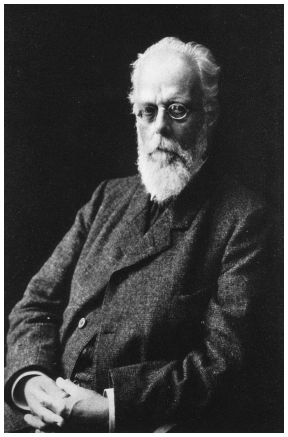
?

August Weismann's theory: Germline vs. soma

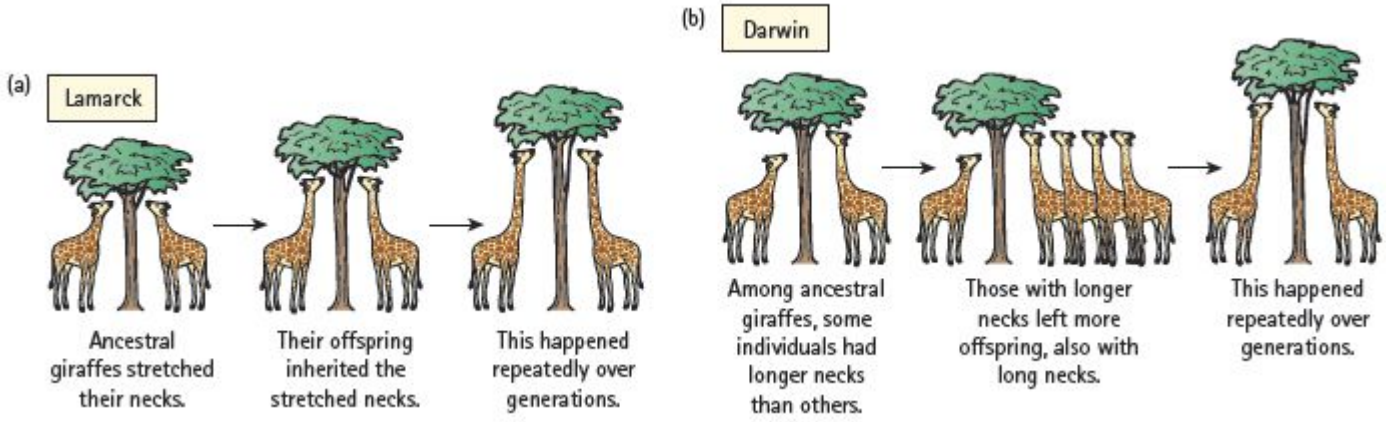
One of the greatest 19th century evolutionary biologist

He was one (of the few) early supporter of Darwin's theory of evolution ("On the Validity of the Darwinian Theory", Weismann, 1868)

He put a final end to the theory of Lamarck and the inheritance of acquired characteristics



August Weismann
(1834-1914)



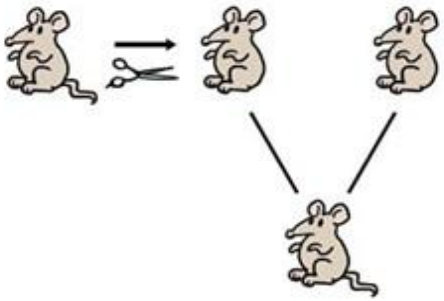
Theory of natural selection (Darwin, 1859)
Theory of inheritance (Weismann, 1892)
("*continuity of the germ plasm*" = germ cell)

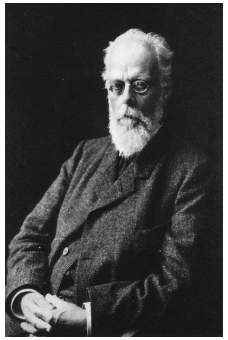
Courtesy of Visual Image Presentations/National Libary of Medicine.

Inheritance of acquired characteristics
("Lamarckism", J.L. Marks 1832 caricature)

Weismann's theory: Germline vs. soma

Study of the inheritance of mutilations
(Weismann, 1888)





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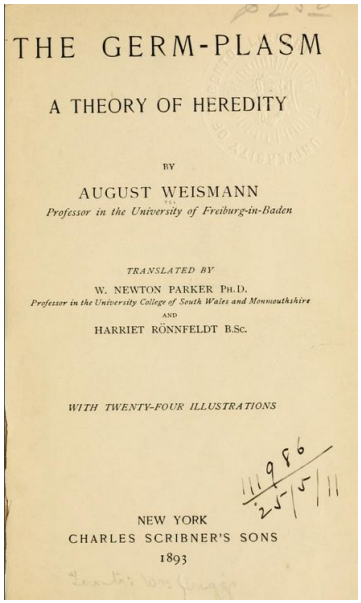
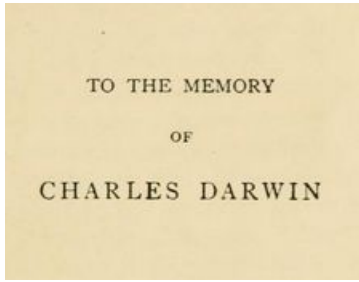
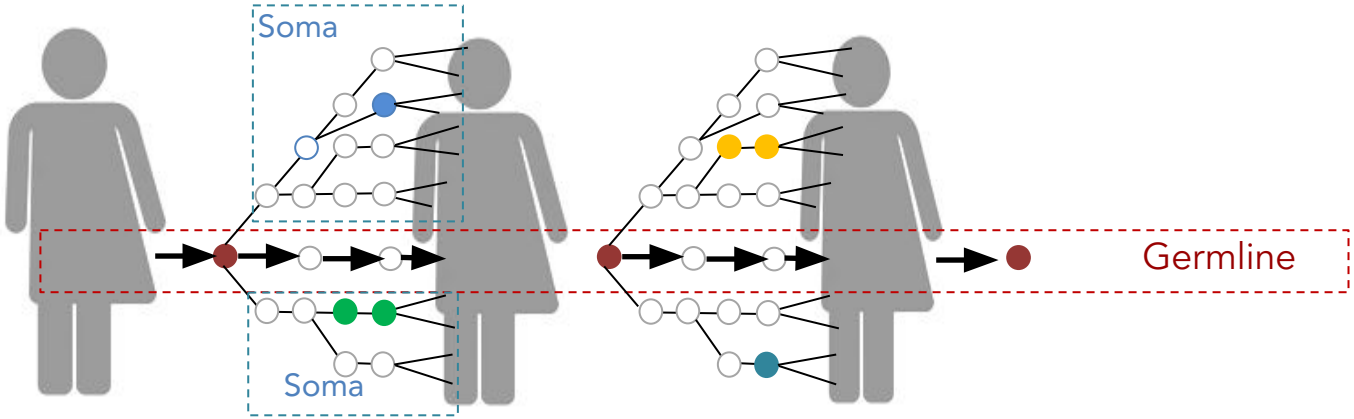




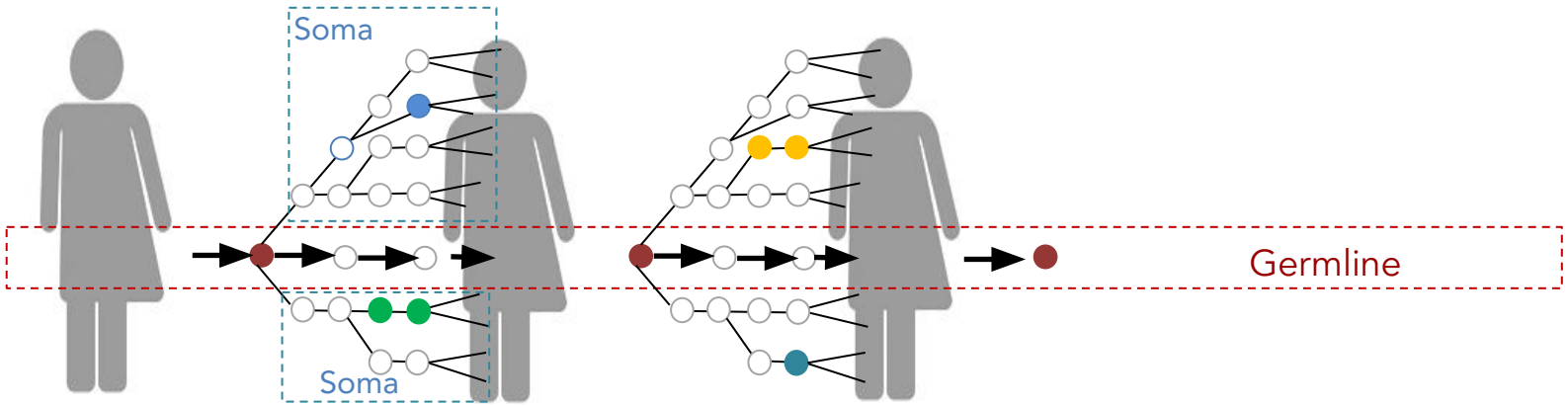


Germline = "immortal" cell lineage

Soma (body)= Somatic cell lineages lost at each generation

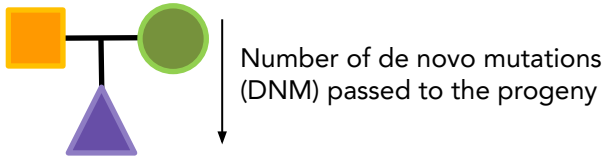
August Weismann's germ plasm theory: hereditary information moves only from germline cells to somatic cells (=somatic mutations are not inherited)

Heritable mutation rates (new mutations on the germline)



Study of heritable mutation rates: Trio sequencing

DNA sequencing of the two parents + one child (~50X) & detection of de novo mutations (DNMs)

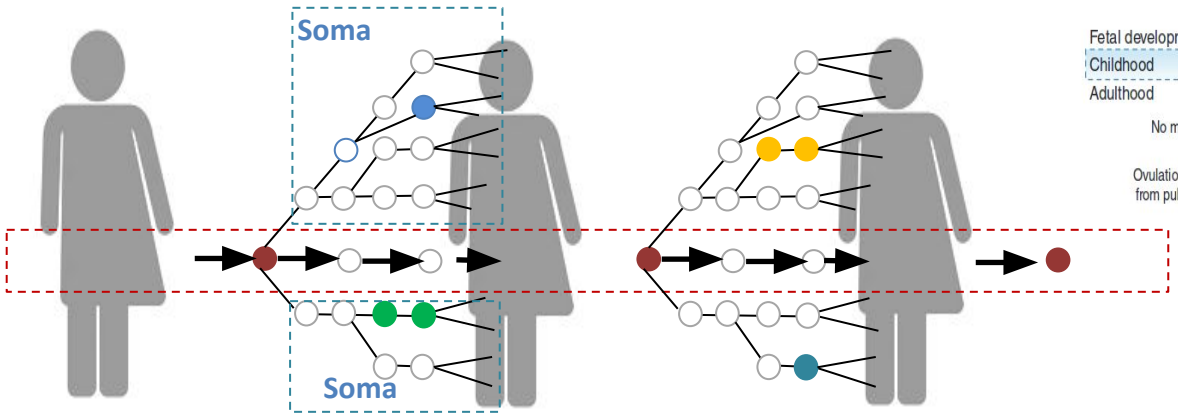


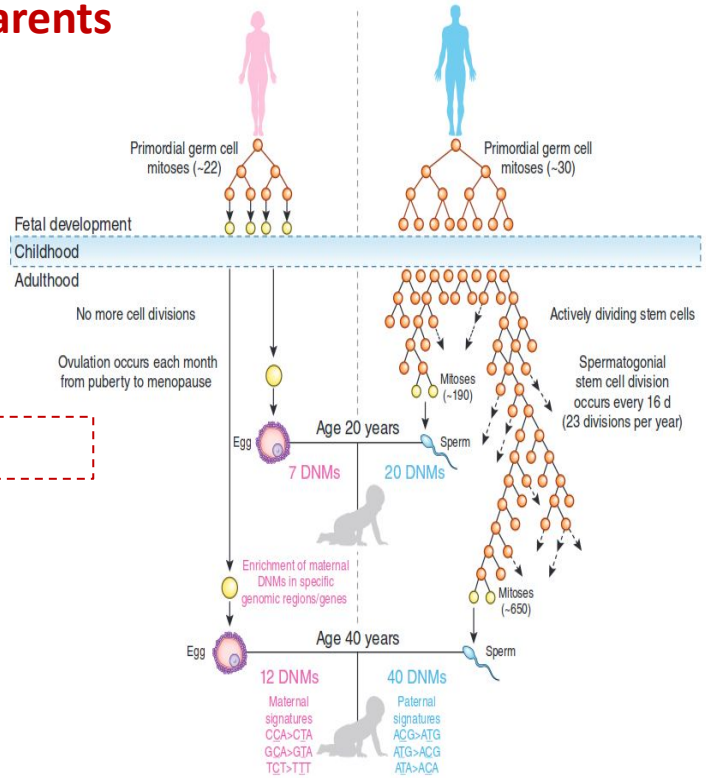
x 1,548 Icelanders families

Jónsson et al. 2017 Nature

New mutations can be easily and unambiguously detected using classic bioinformatic tools (variant callers such as GATK, Samtools, …)

de novo heritable mutations (DNMs) and age of the parents

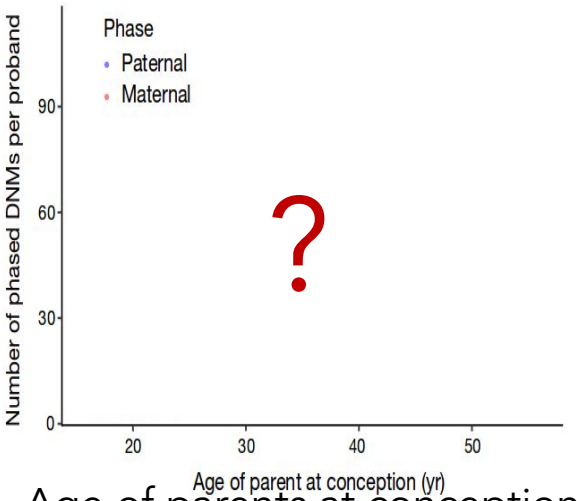




Study of heritable mutation rates: Trio sequencing

Goldmann et al. 2016 Nature Genetics
Goriely 2016 Nature Genetics

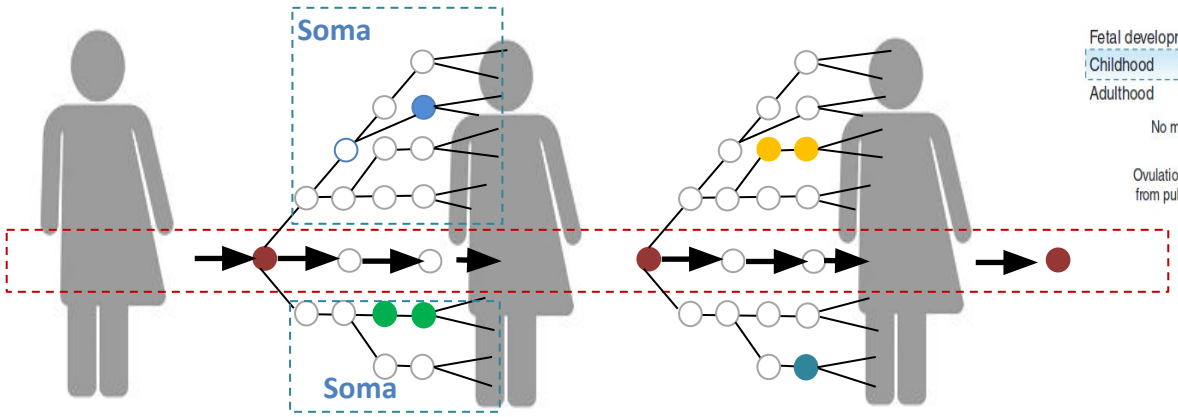
Number of *de novo* mutations identified in the child

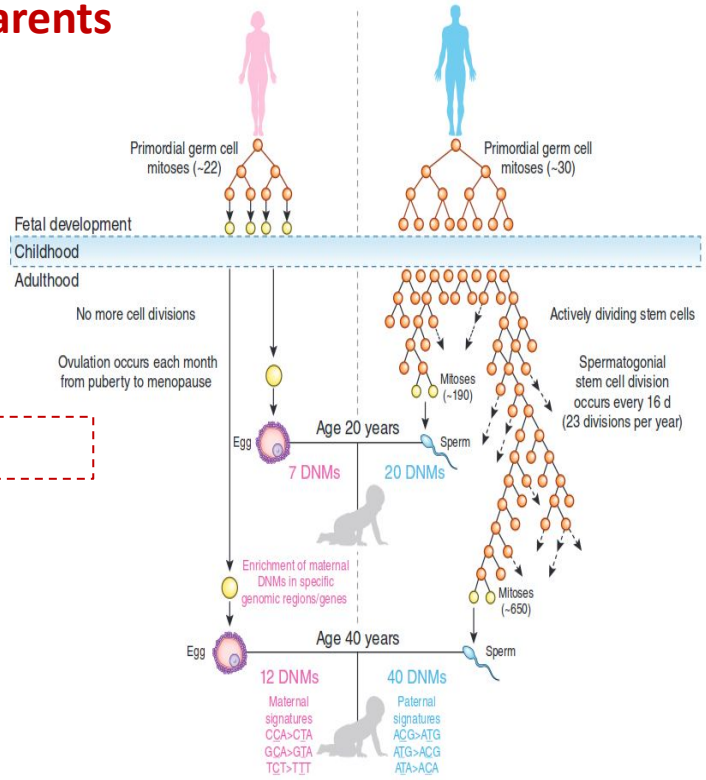


Age of parents at conception of the baby

Jónsson et al. 2017 Nature (see also Kong et al. 2012 Nature)

de novo heritable mutations (DNMs) and age of the parents





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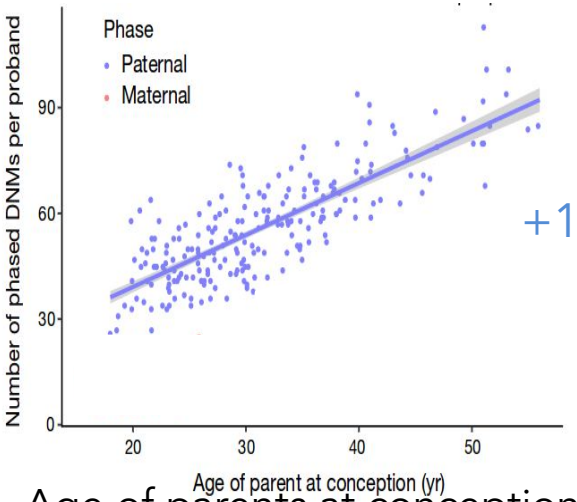
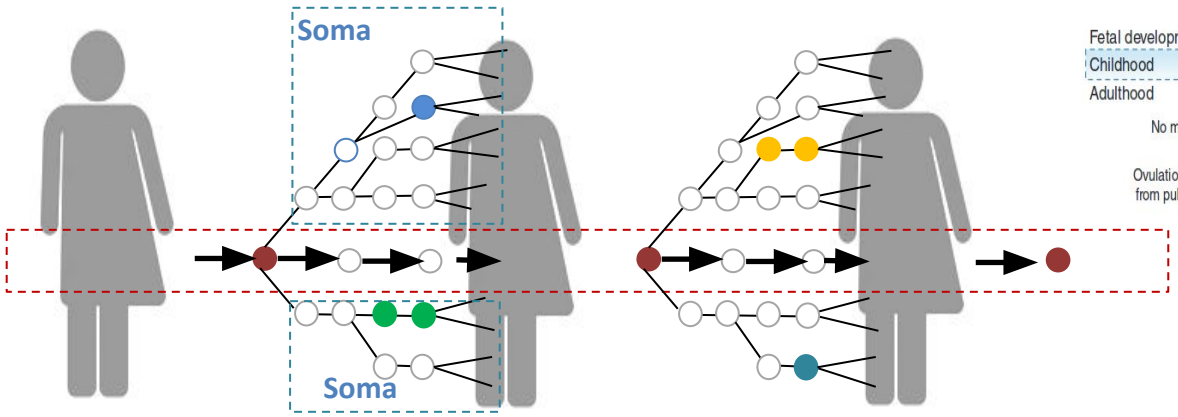


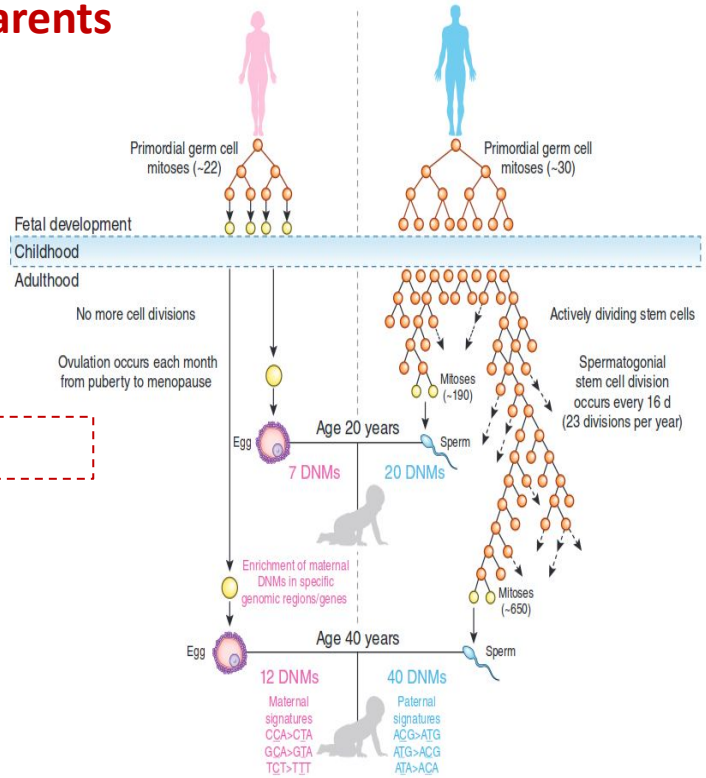
+1.51 DNMs / year

Age of parents at conception of the baby

Jónsson et al. 2017 Nature (see also Kong et al. 2012 Nature)

de novo heritable mutations (DNMs) and age of the parents





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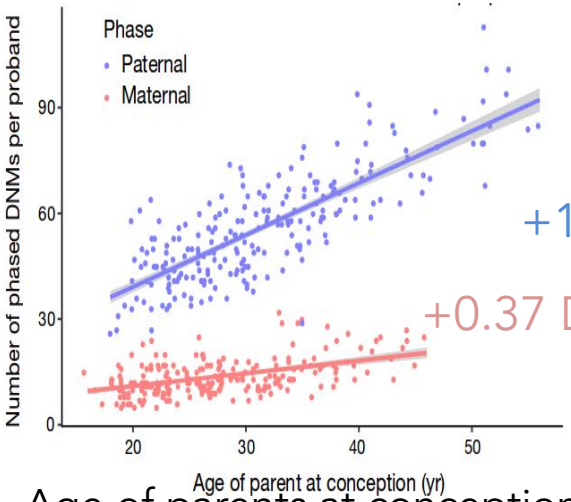


+1.51 DNMs / year

+0.37 DNMs / year

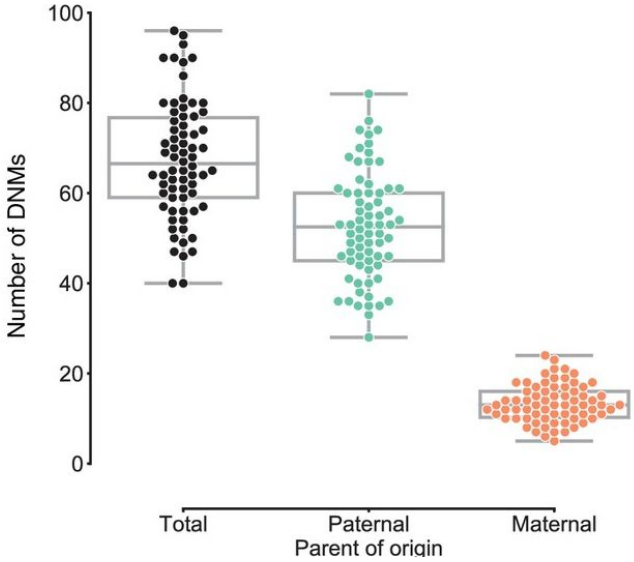
Age of parents at conception of the baby

Jónsson et al. 2017 Nature (see also Kong et al. 2012 Nature)

Summary: animal germline mutations (heritable mutations)

Sex-specific pattern:

Human germline (*i.e.* heritable) mutations disproportionately occur in males



Sasani et al. 2019 eLife

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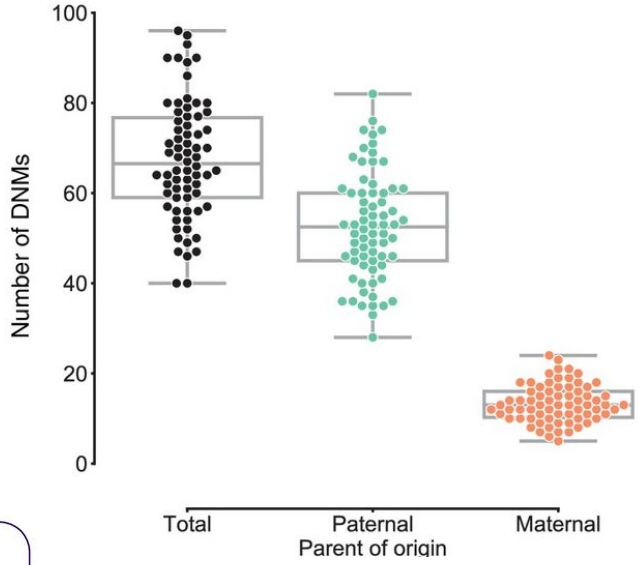
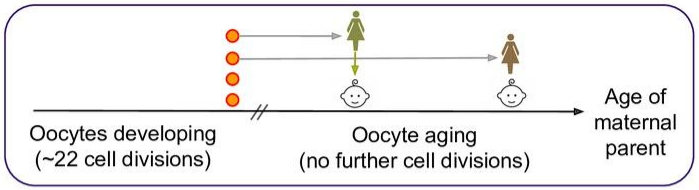
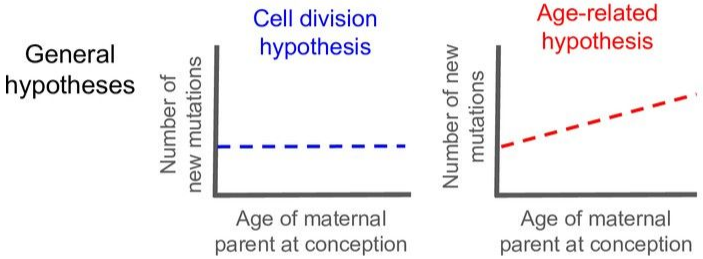


Sasani et al. 2019 eLife

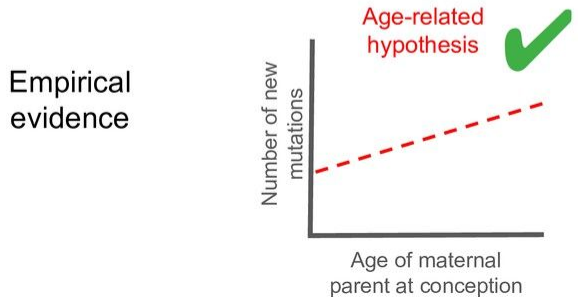
Age-specific pattern:

More mutations with age





Mutations of maternal origin support that they are associated with errors of the DNA repair machinery, not due to errors during the DNA replication!



Unrepaired damage accumulating with age

Leroy 2023, eLife

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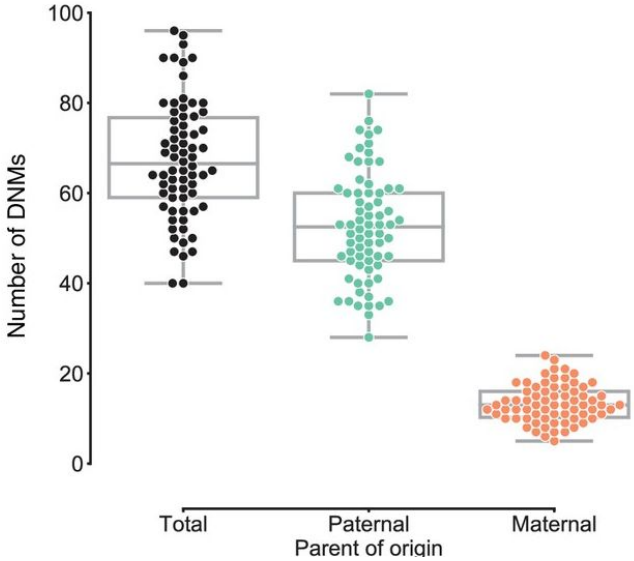


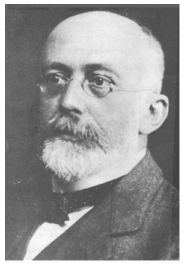
Sasani et al. 2019 eLife

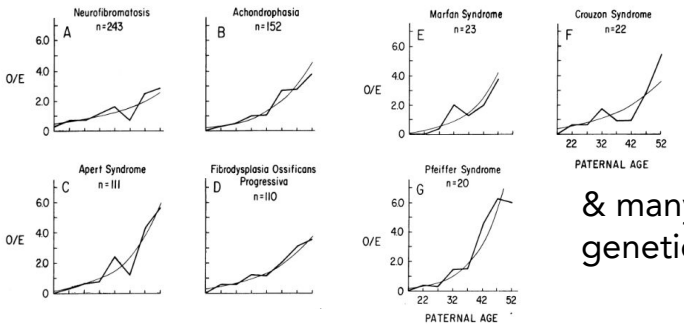
Age-specific pattern:

More mutations with age

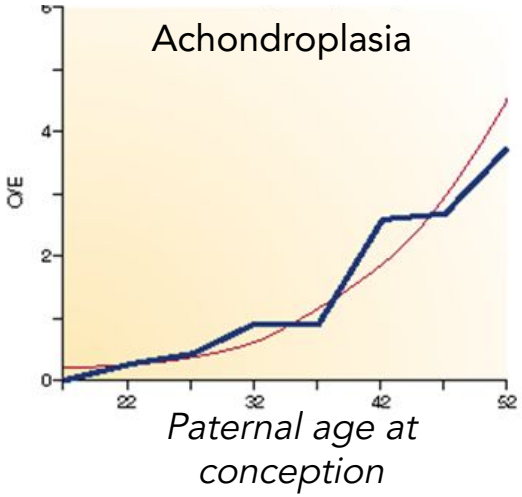
Medical consequences in humans: Sex*Age-specific pattern

"If a more exact analysis of birth order were indeed to confirm a high incidence in last-born children, this would speak for the formation of the initial predisposition for dwarfism by mutation."
Wilhelm Weinberg, 1912





& many other genetic disorders…



Crow, 2000 Nature Review Genetics

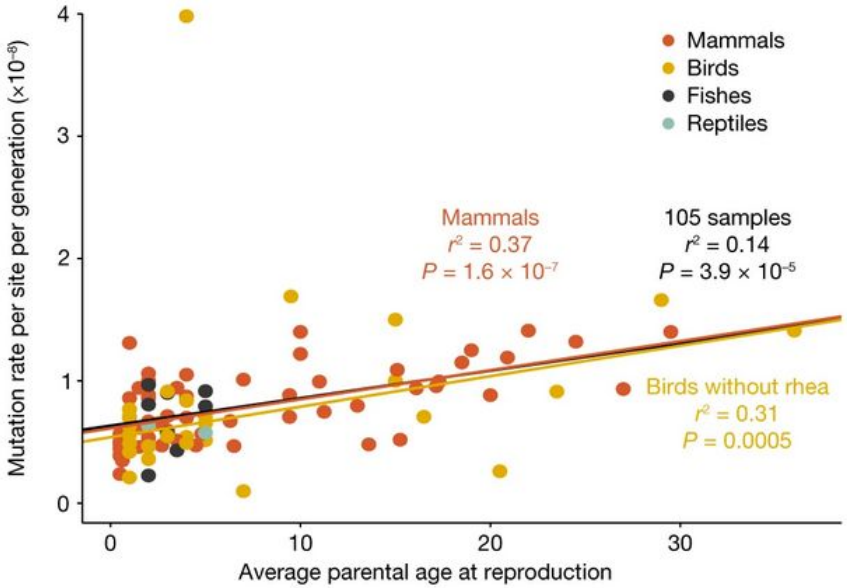
Risch et al. 1987 American journal of human genetics

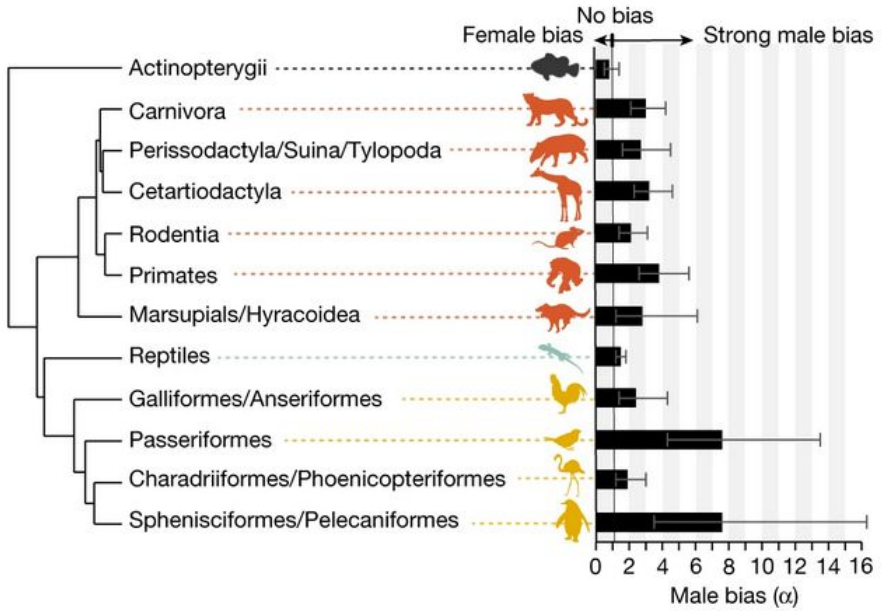
Summary: animal germline mutations

A calm couple of
Chrysemys picta

Sex- & age-specific pattern

True in many animals, not only humans, albeit not all



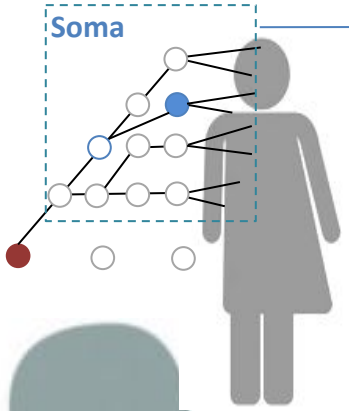


Bergeron *et al.* 2023 Nature

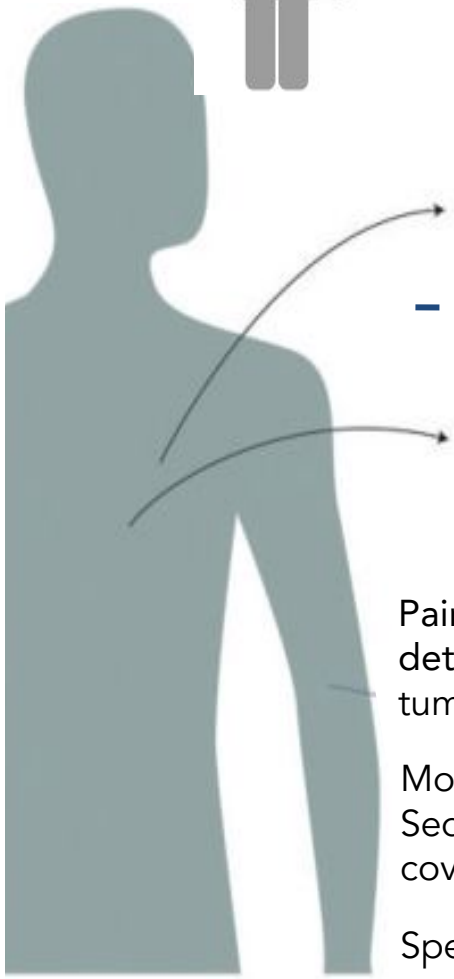
In mammals (and in most animals)
Germline mutations = meiotic mutations + mitotic mutations (accumulating with age) on germinal cells

Ok for germline mutations, but what about somatic mutations?

Somatic mutations and cancers



Not heritable but still important!



Pairwise mutation detection:
tumor *vs.* normal samples

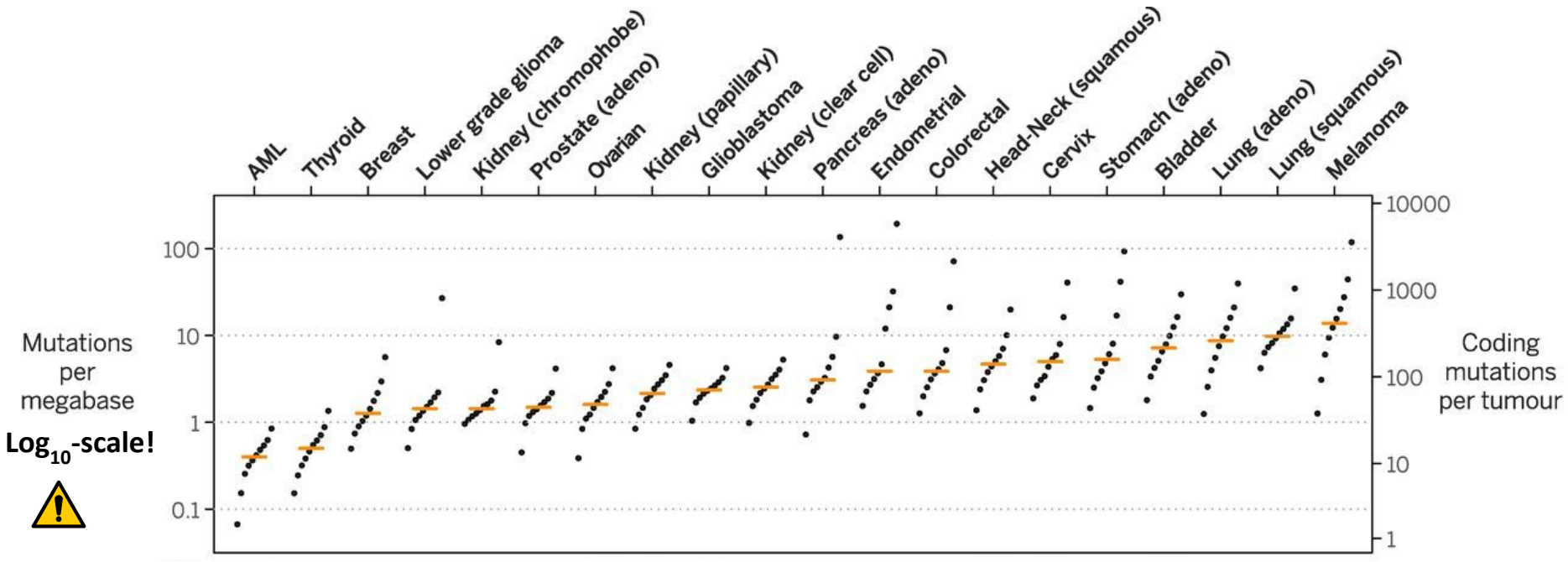
More challenging:
Sequencing at very high coverage (100s - 1000s X)

Specific bioinformatic tools

A	G	T	G	A		A	C	G	A	T
A	G	T	G	A		A	C	G	A	T
A	G	T	G	A		A	C	T	A	T
A	G	T	G	A		A	C	G	A	T
A	C	T	G	A		A	C	G	A	T
A	G	T	G	A		A	C	T	A	T
A	C	T	G	A		A	C	G	A	T
A	G	T	G	A		A	C	T	A	T
A	G	T	G	A		A	C	G	A	T
A	G	T	G	A		A	C	G	A	T
A	G	T	G	A		A	C	G	A	T
A	G	T	G	A		A	C	T	A	T
A	G	T	G	A		A	C	G	A	T
A	G	T	G	A		A	C	G	A	T
A	G	T	G	A		A	C	G	A	T

Somatic mutations and cancers

Frequency of occurrence of new mutations

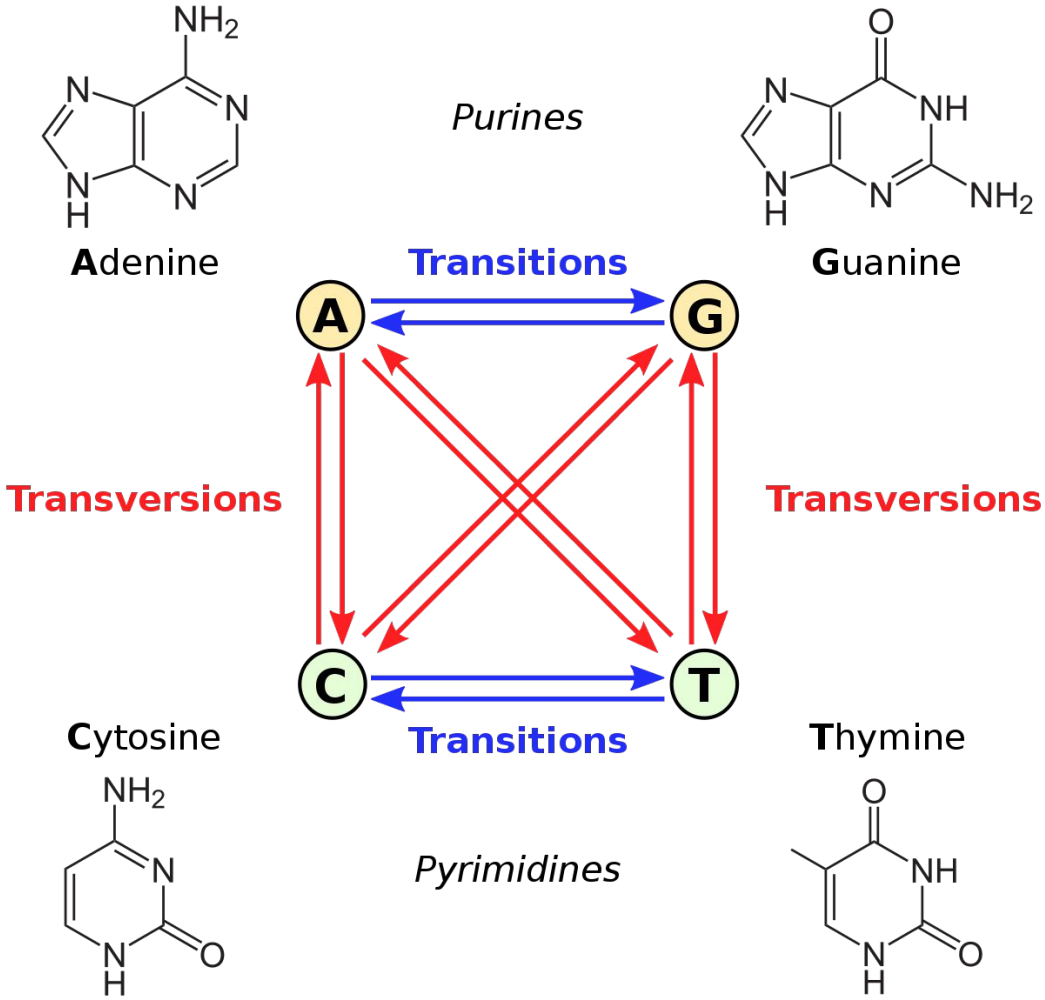


Mutation rates are highly variable depending on the tumor samples, because mutations do <u>not</u> occur at the same pace depending on the tissues

-> Importance of mutagens, *i.e.* UV for melanoma!

Martincorena & Campbell, 2015 Science

Mutational signatures (mutation spectra)



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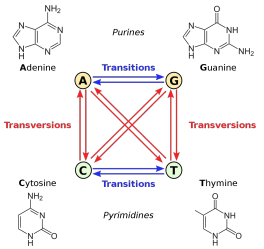

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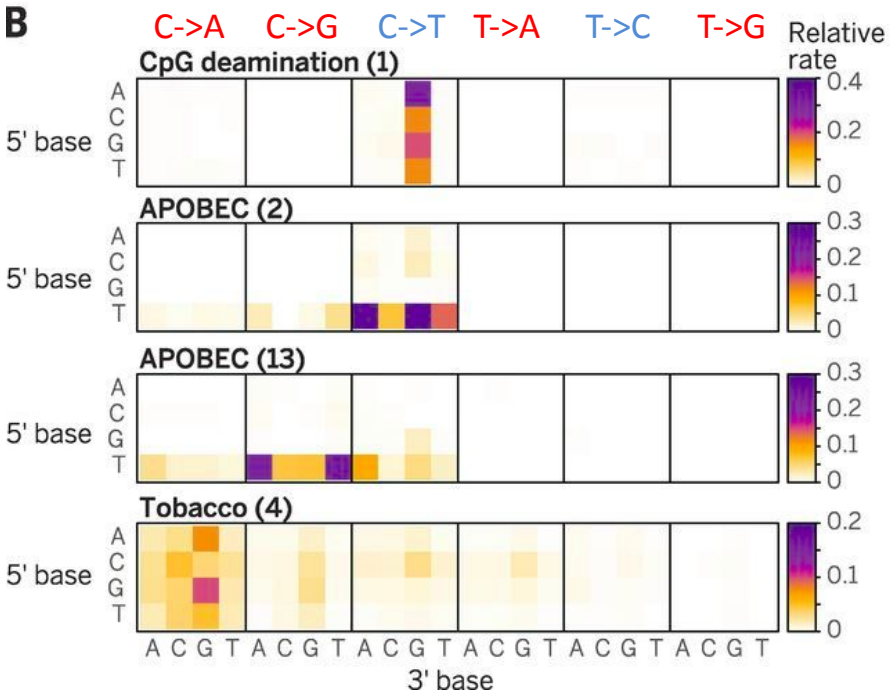
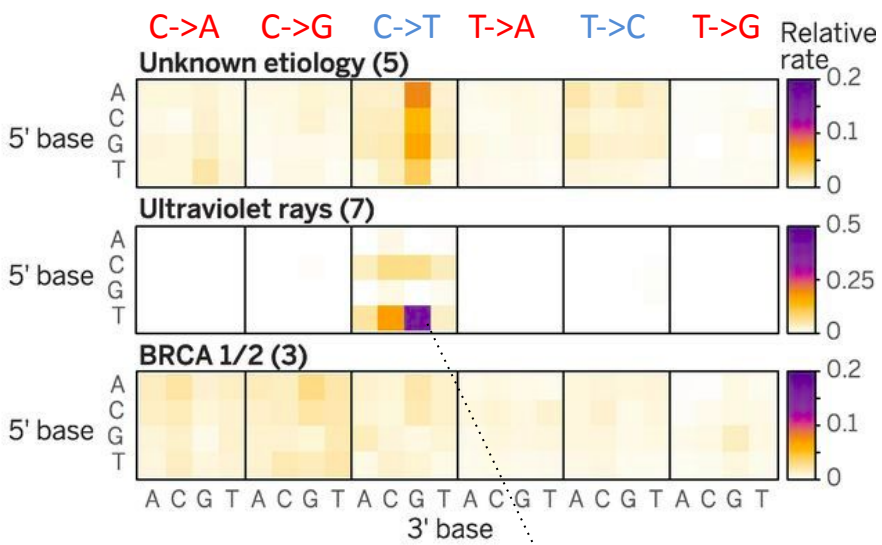




~ Half of the UV-induced mutations in humans are TCG -> TTG

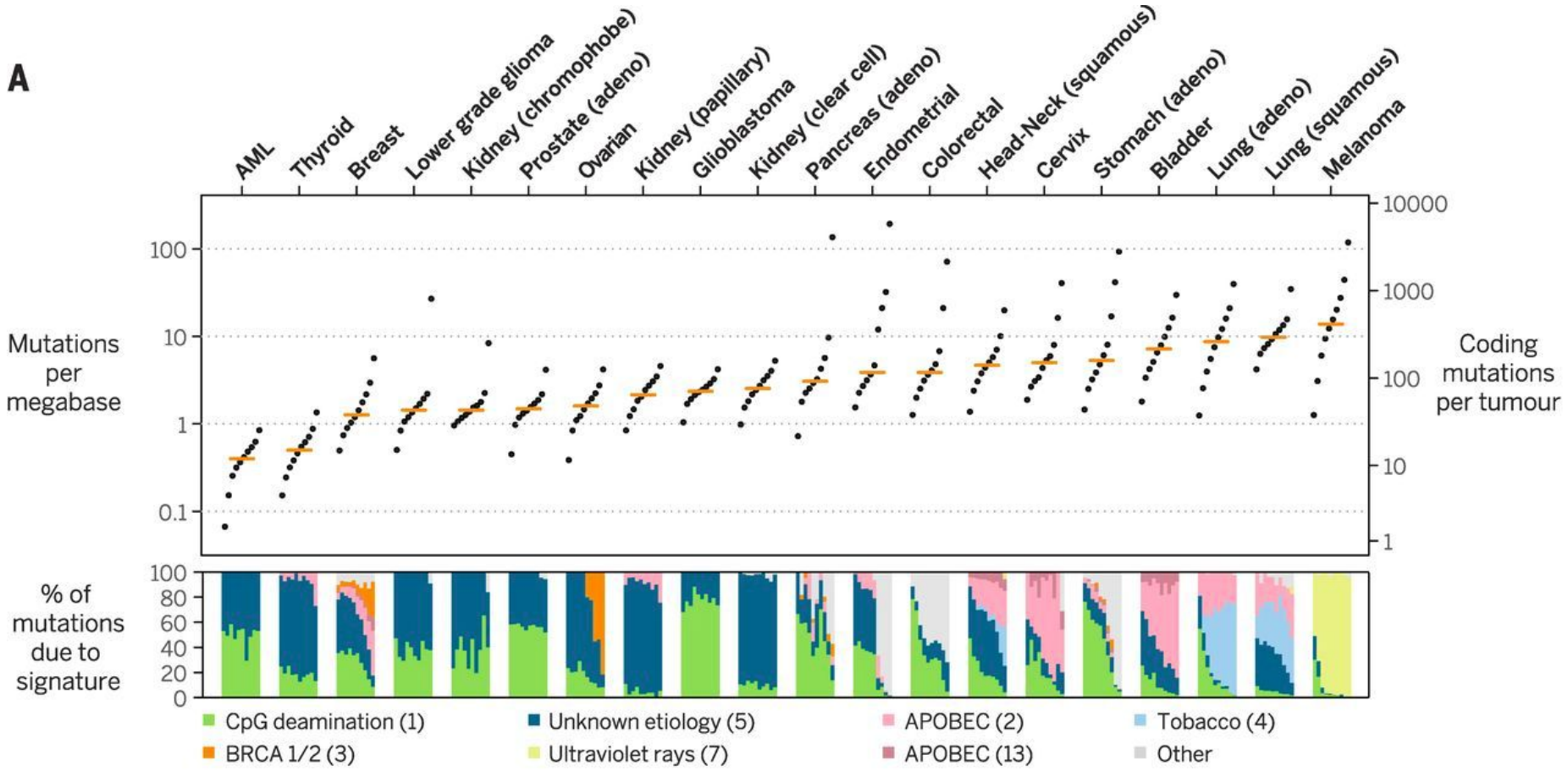
Mutation is a random process but highly dependent on the genomic context

Importance of mutagens, *i.e.* UV for melanoma!

Modified from Martincorena & Campbell, 2015 Science

Somatic mutations and cancers

Frequency of occurrence and mutational signatures

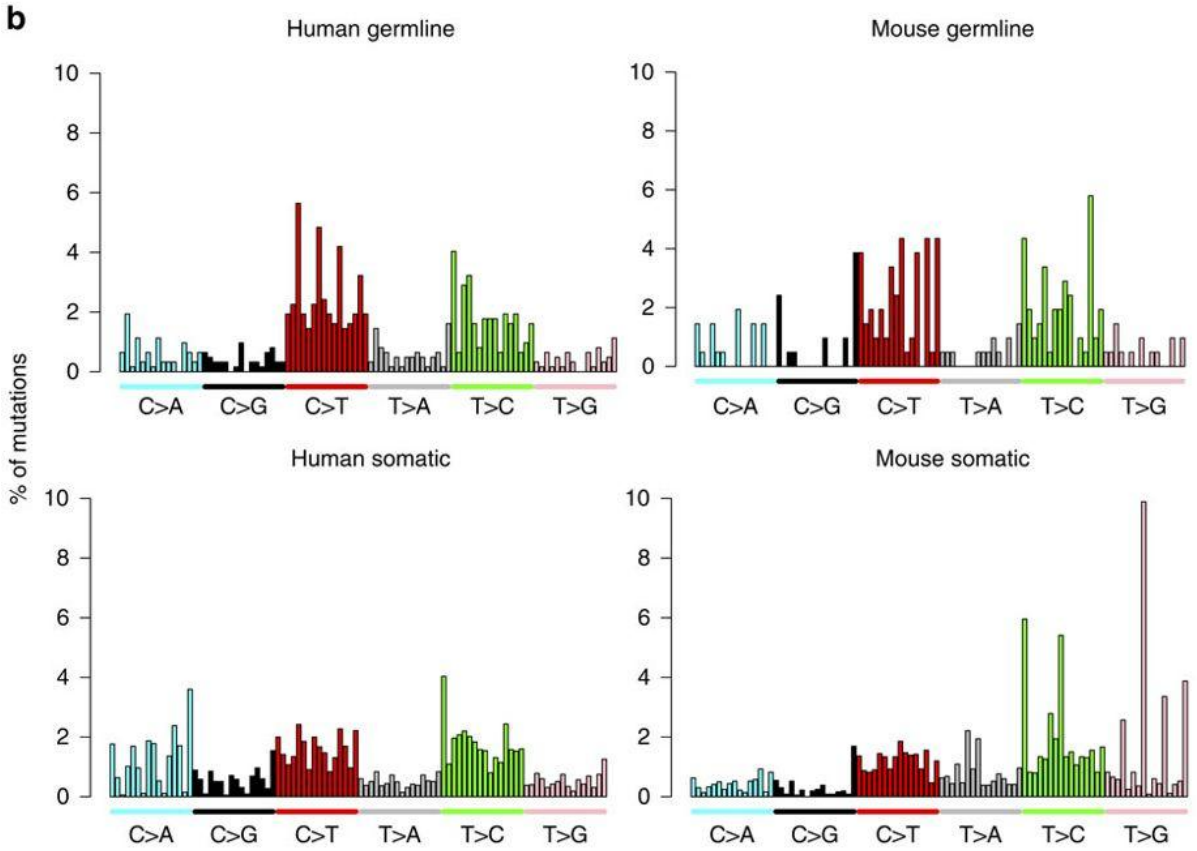


Summary: somatic and germline mutations

Mutation is a random process, but…

… the probability for a mutation to happen is non-random, shaped by the genomic context (true on both the germline and the somatic tissues)

… probabilities which depend on the genomic context (*i.e.* mutation spectra) evolve through time. Both rates and mutation spectra can be seen as evolvable traits.



Milholland et al. 2017 Nature communications

Summary: somatic and germline mutations

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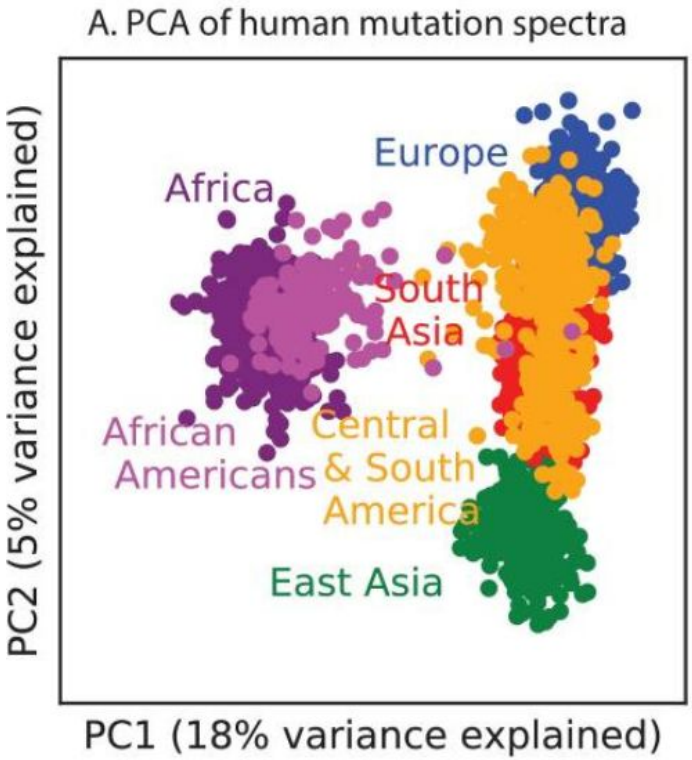
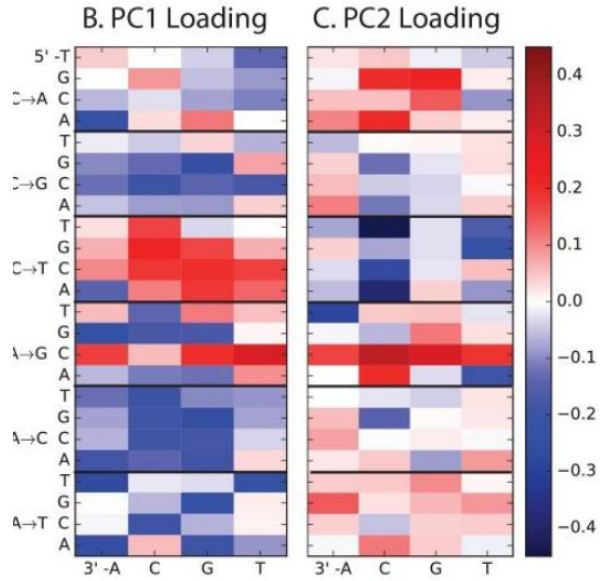
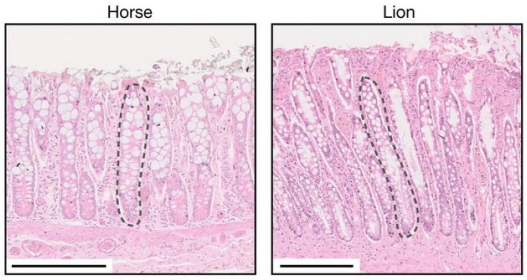
Even at relatively short evolutionary time, it seems! Here an example for the evolution of the germline mutation spectra in humans



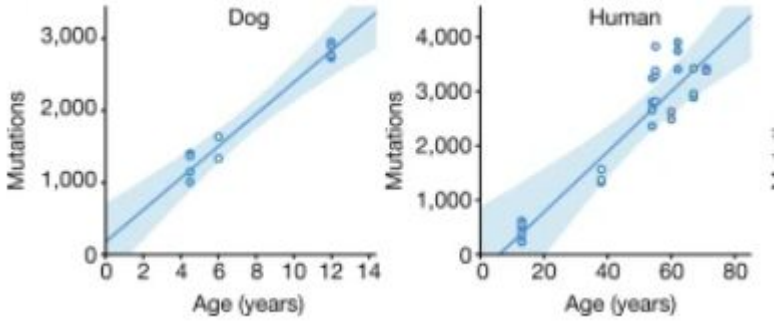


Harris & Pritchard 2017, eLife

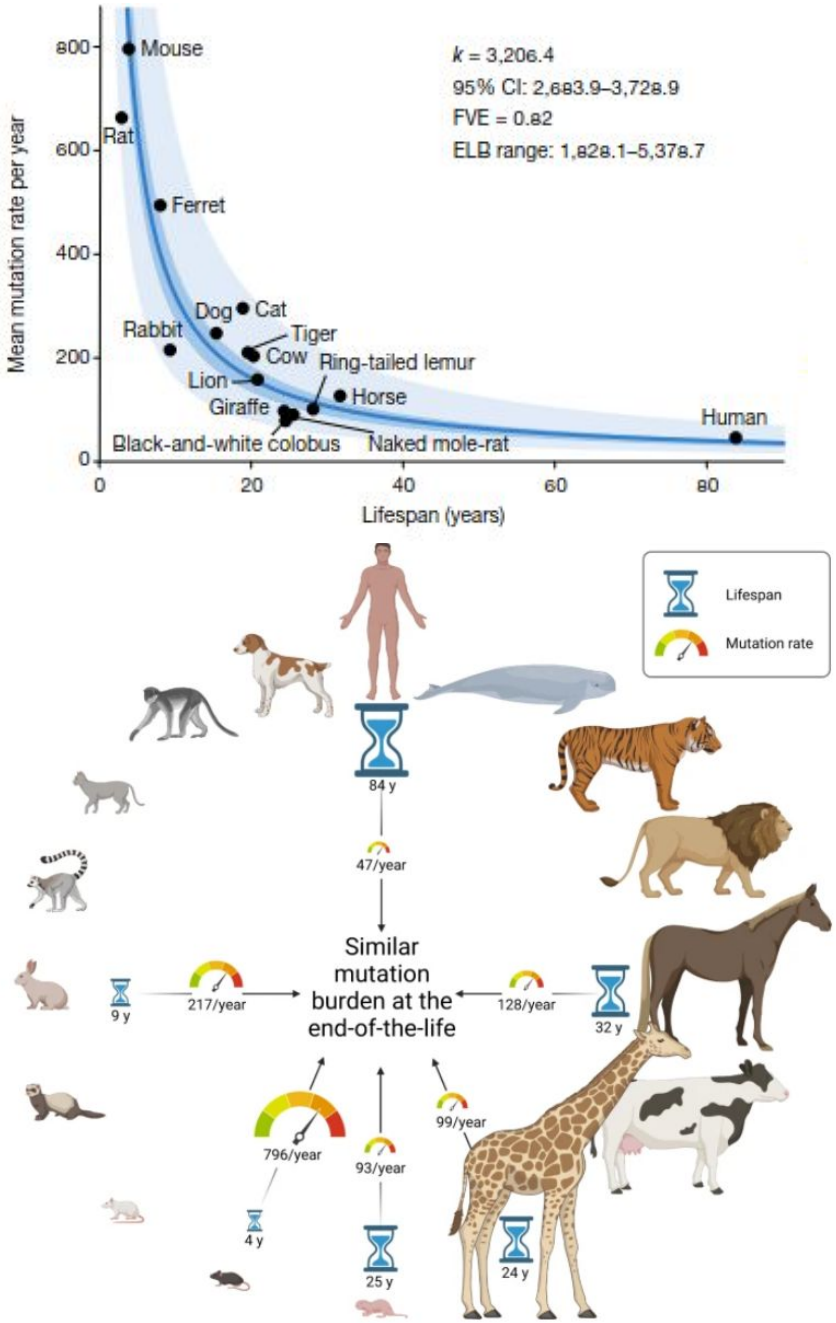
Perspective: somatic rates and life span



208 individual intestinal crypts from 56 individuals across 16 species



Recent investigations suggest that somatic mutation rates are (also) evolutionarily constrained and may be a contributing factor in ageing



Cagan et al. 2022 Nature; Cremer et al. 2022 Signal Transduction and Targeted Therapy

Heritable and non-heritable mutation detection in animals and plants

Ron and Joyce Bond
(UK's (World's?) oldest living married couple)

« The Major Oak », Sherwood Forest, Nottinghamshire, England (800-1,000 years old, UK's most visited tree)

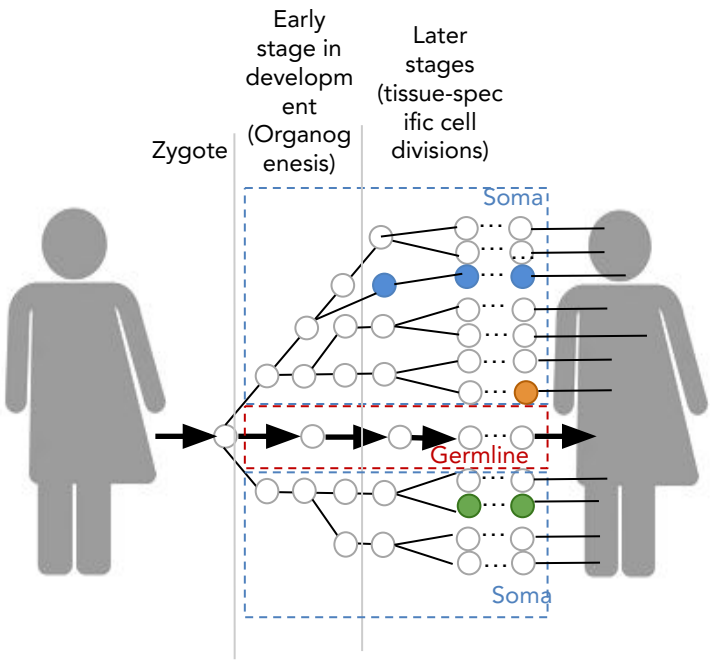
Heritable mutations in animals = germline mutations = meiotic mutations + mitotic mutations on germinal cells

?

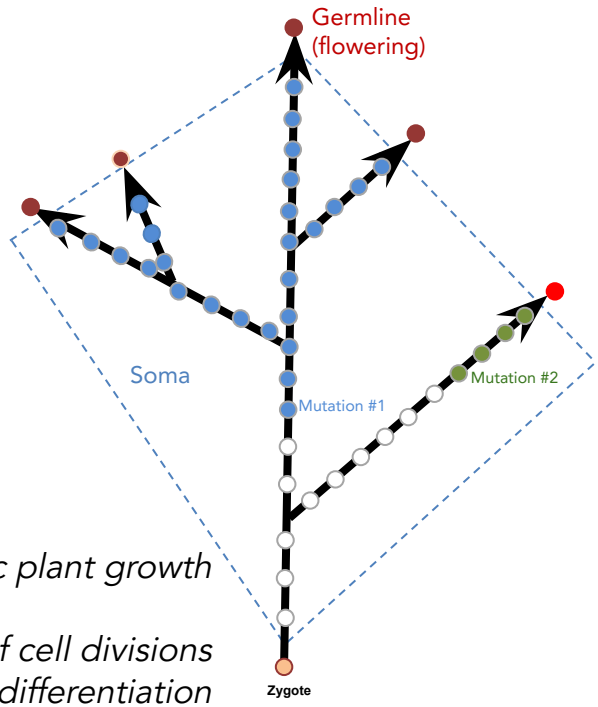
Other somatic mutations are not heritable

General expectation: plants depart from the Weismann's theory

Animal model



Plant model



Somatic plant growth

millions of cell divisions before the differentiation of the germline

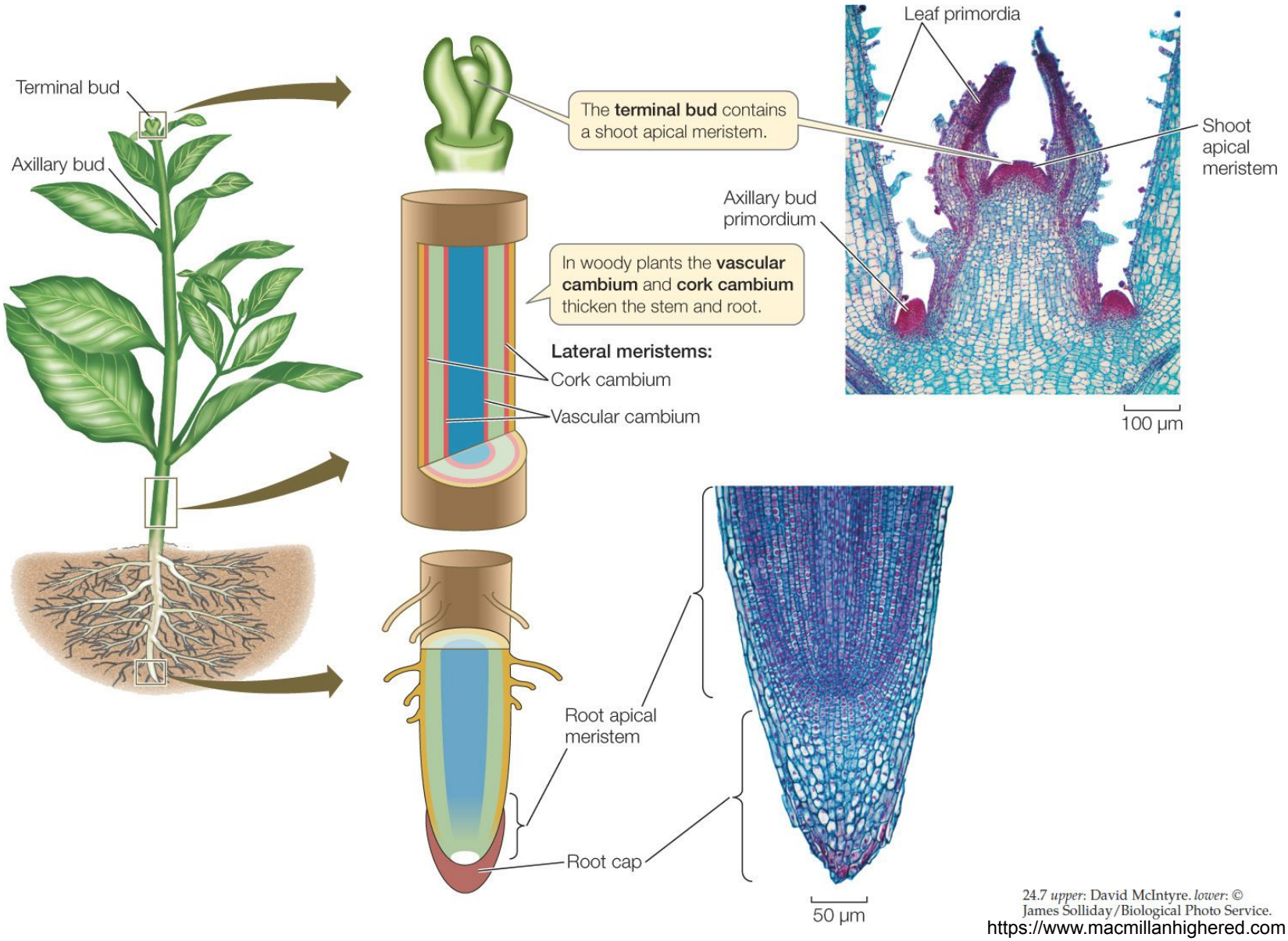
Unlike animals, somatic mutation could be passed to the progeny in plants (late germline segregation)

⚠ <u>This is a general hypothesis</u>

I will detail the empirical evidence supporting this hypothesis (or not)

General expectations for plants

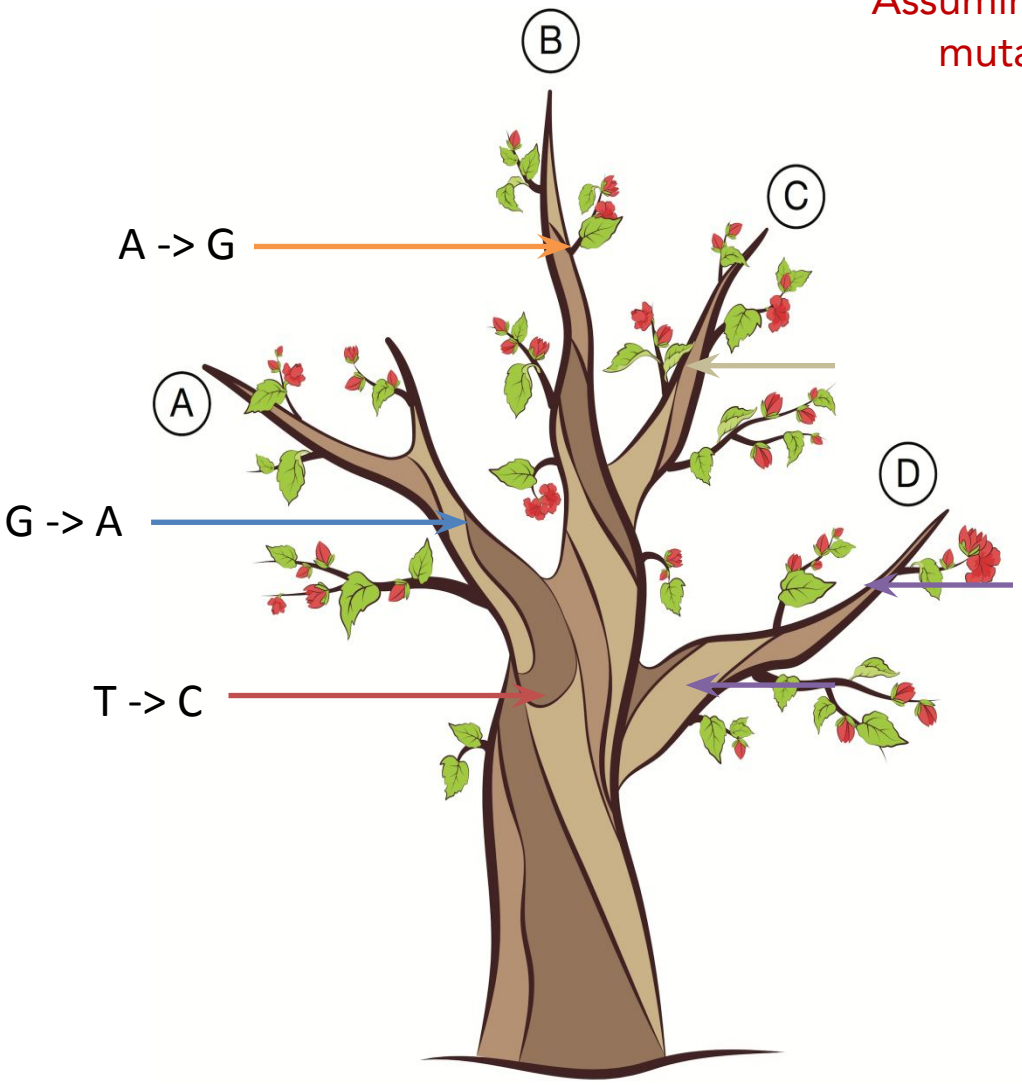
Before to start, just a short recap on how plants grow…



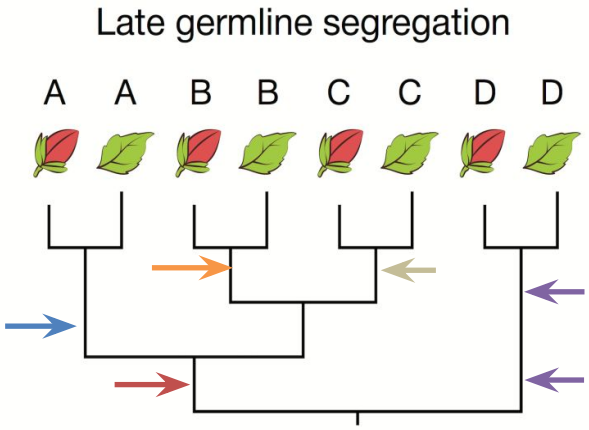
24.7 *upper*: David McIntyre. *lower*: © James Solliday/Biological Photo Service.

https://www.macmillanhighered.com (24.2)

General expectations for plants



Assuming a late germline segregation for plants, mutations accumulate along growth axes!

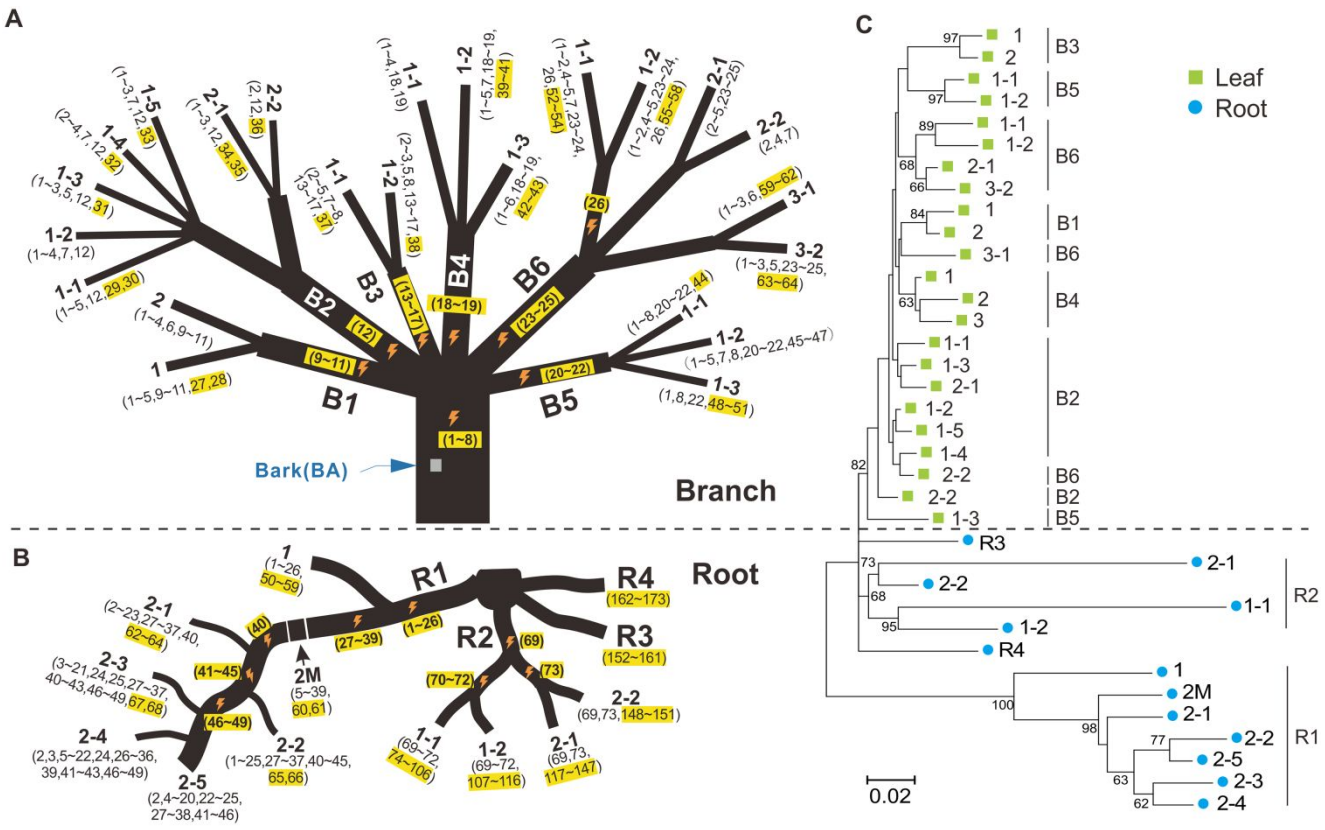


Following this view, a tree is also a … phylogenetic tree!

Modified from Robert Lanfear, 2018 PLoS Biology

A typical example in *Prunus*

36 samples from a peach tree (13 from roots, 23 from shoots)!



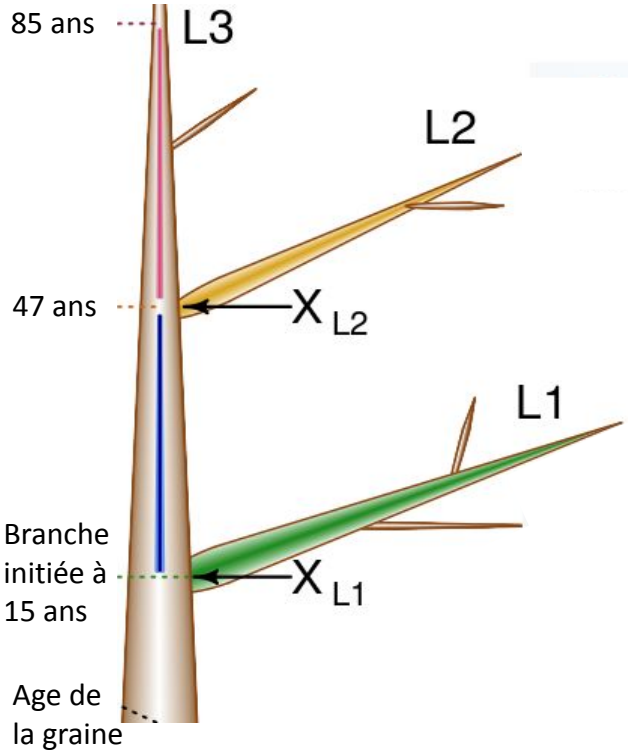
Lower mutation rates in shoots: a way to keep heritable mutation rates under control?

Far more mutations detected in roots than in shoots!

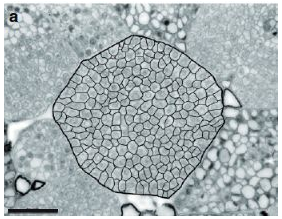
Samples	Diameter of the trunk (cm)	Estimated age (years)	DNA source	Sequenced samples	Accumulated mutations	
					Average observed	Normalized rate ($\times 10^{-9}$ per bp per year)[a]
PXL[c]	11.1	21	Leaf	23	3.74	0.52
			Root[d]	13	29.8	4.06

Wang et al. 2019 PLoS Biology

First empirical evidences: “3P” oak tree in Pierroton



3 samples sequenced at 160X



Schmid-Siegert et al. 2017, Nature plants

When a new somatic mutation occurs: freq (alt) = 1 / 2N meristematic cells

(assuming 20 meristematic cells, freq ~ 0.025)

Require variant calling using software adapted for low-frequency mutations (similar to somatic mutation in cancer)

Plomion et al. 2018 Nature Plants

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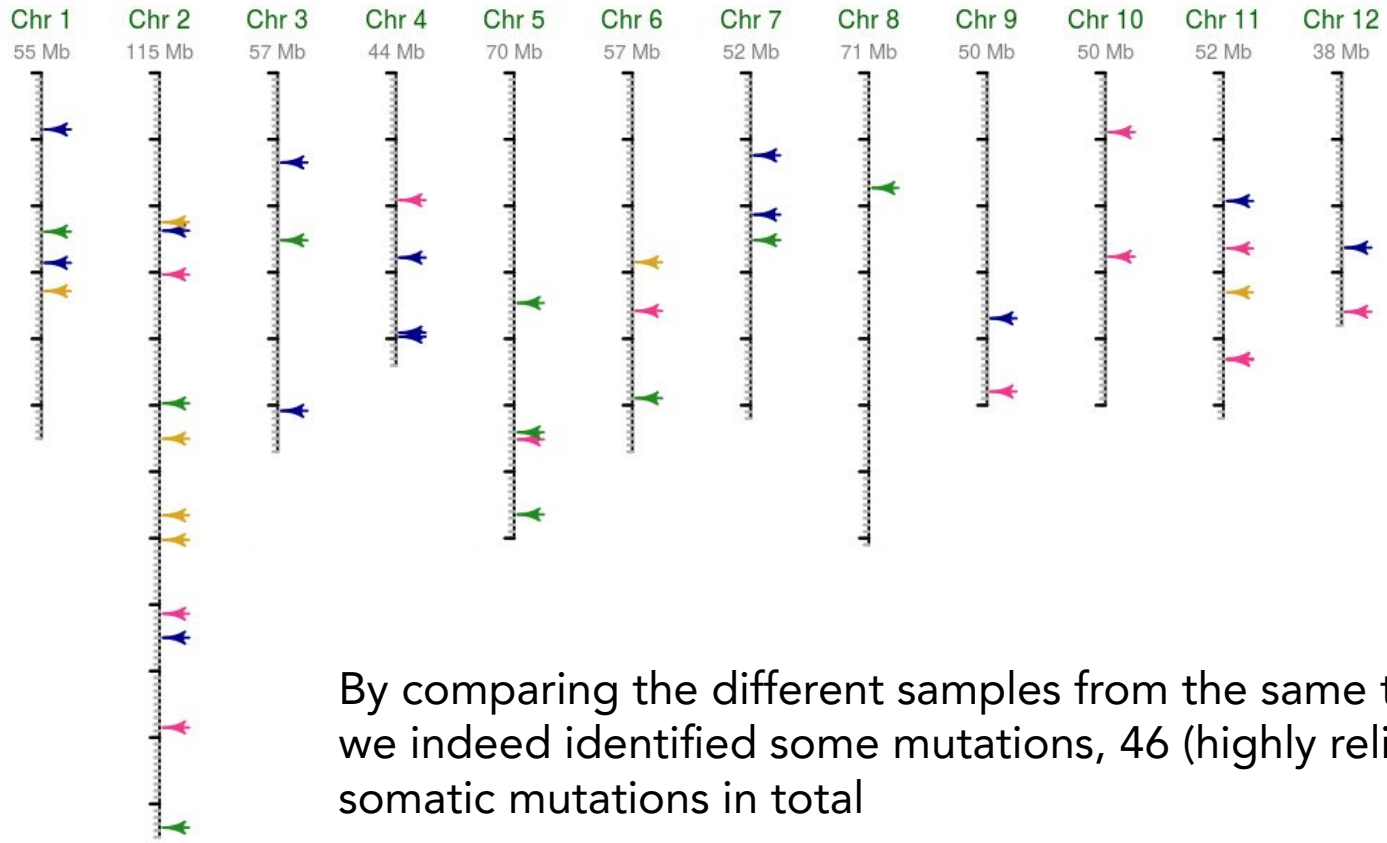

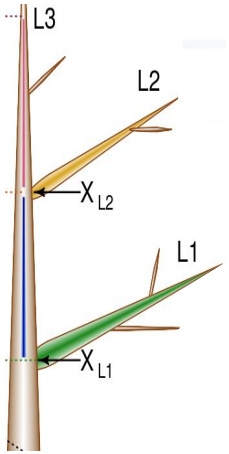

By comparing the different samples from the same tree, we indeed identified some mutations, 46 (highly reliable) somatic mutations in total

Plomion et al. 2018 Nature Plants

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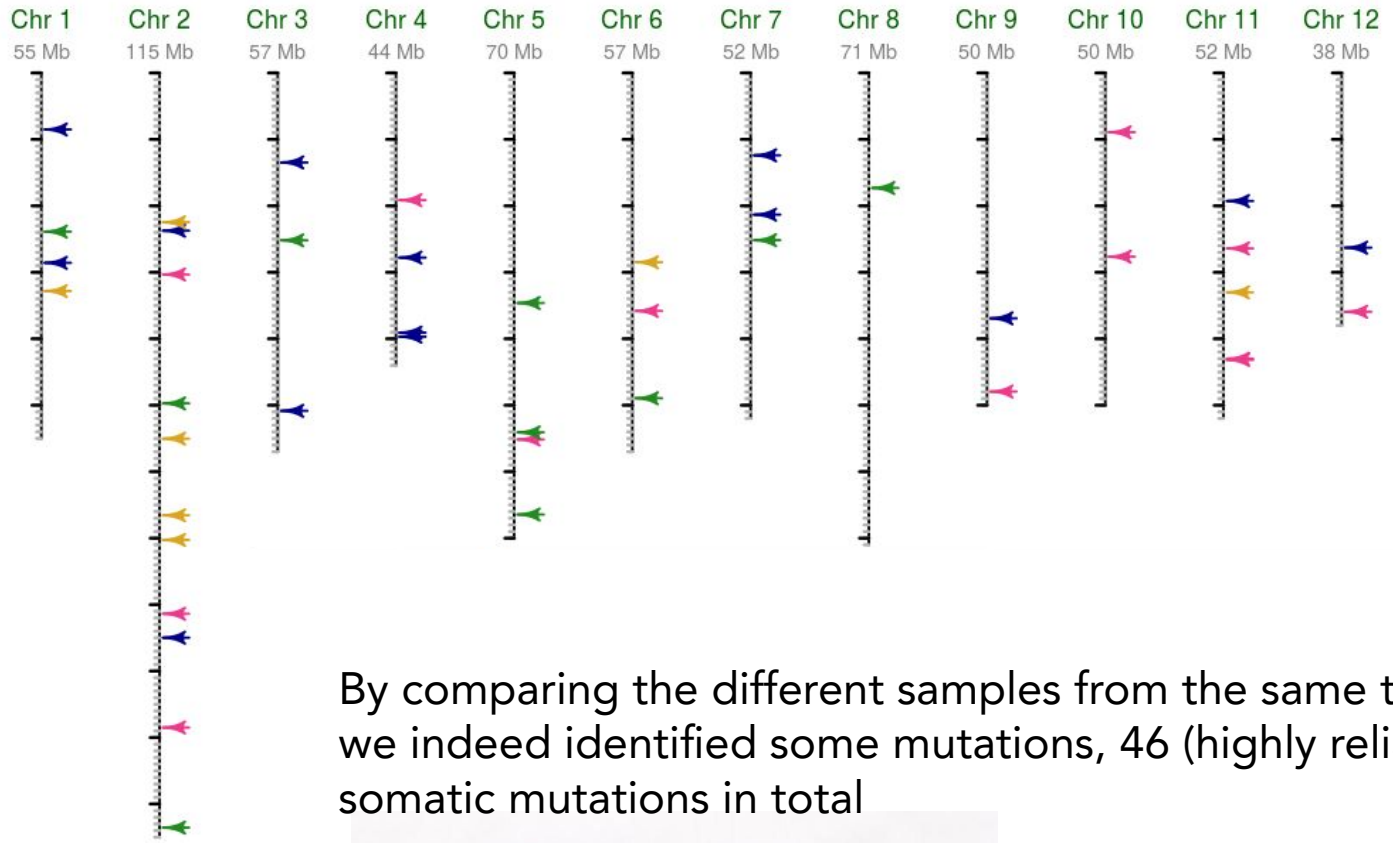

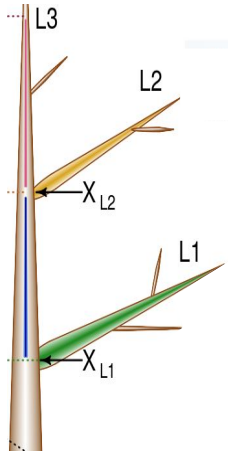

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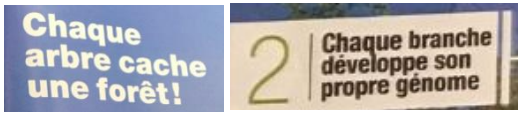
Extremely rare events

46 mutations / 7,5 x 10^8 bp!
(for a 100-year old tree)

Study of the mutation process



Science & Vie, octobre 2018

Plomion et al. 2018 Nature Plants

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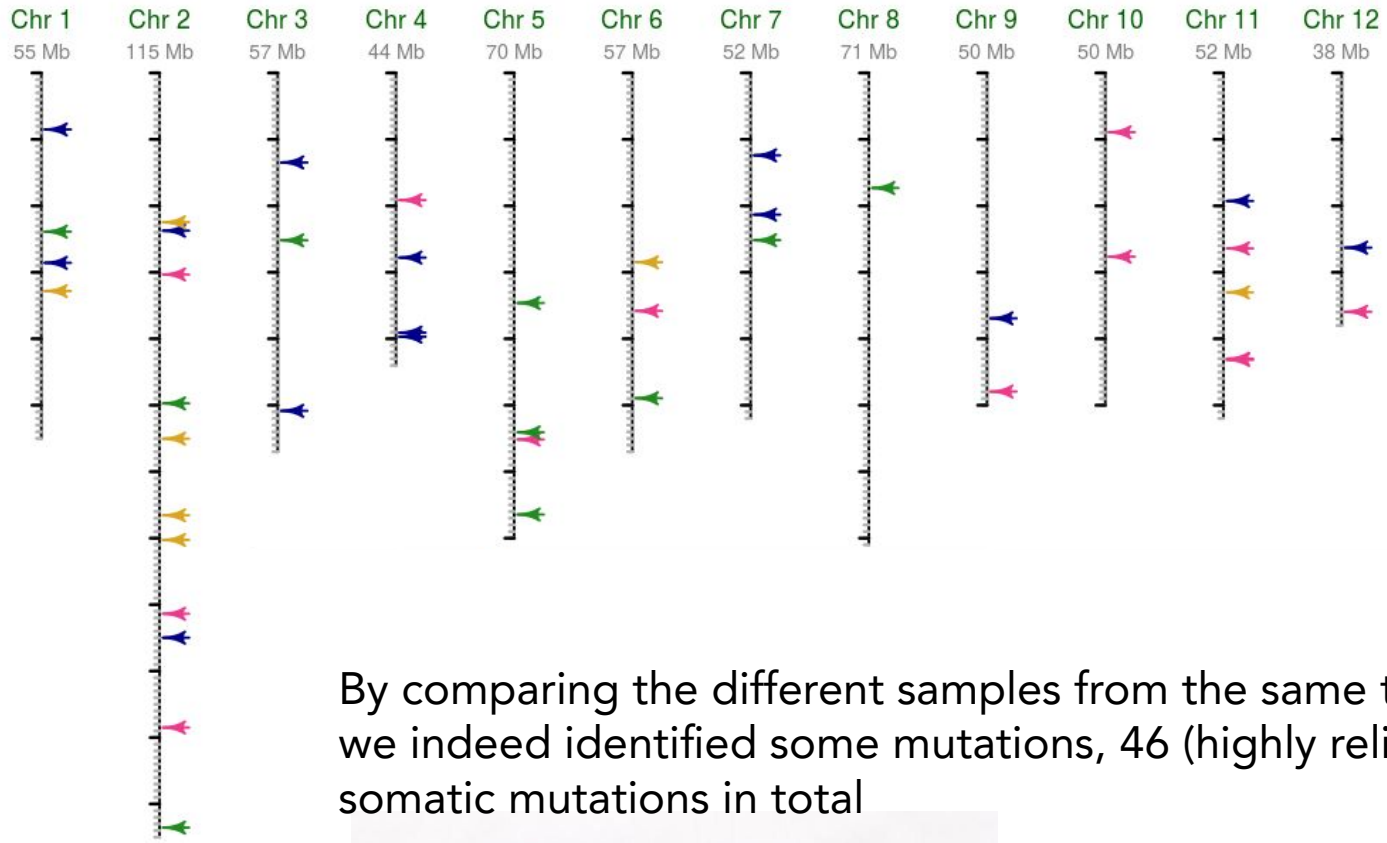

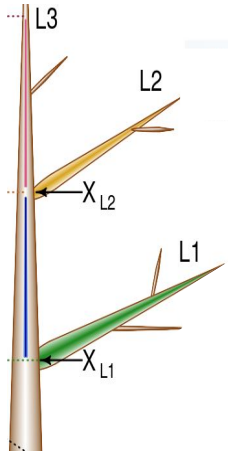

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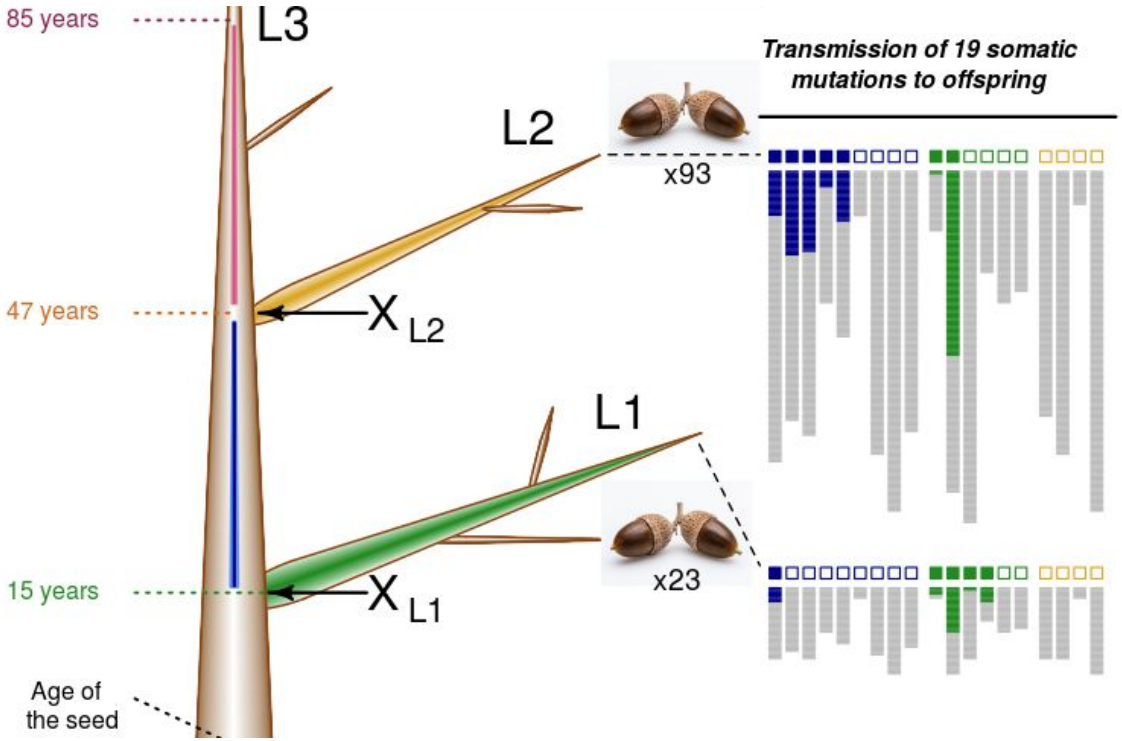
Are somatic mutations passed to the progeny?



~50% of the mutations tested were found to be transmitted to the next generation

In agreement with the general hypothesis for plants

Plomion et al. 2018 Nature Plants

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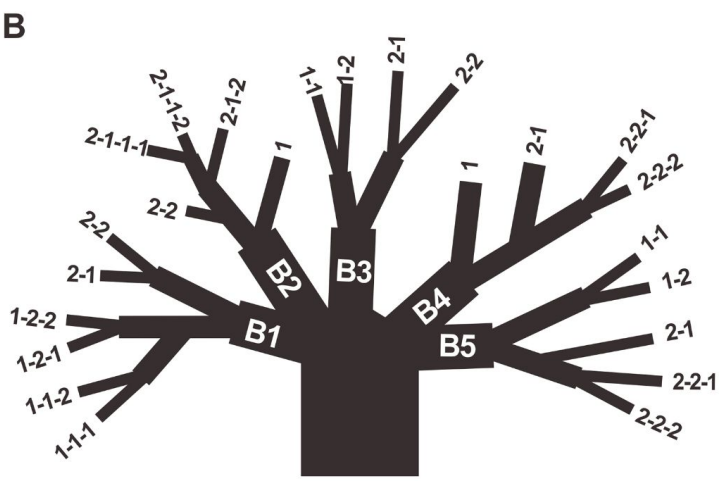
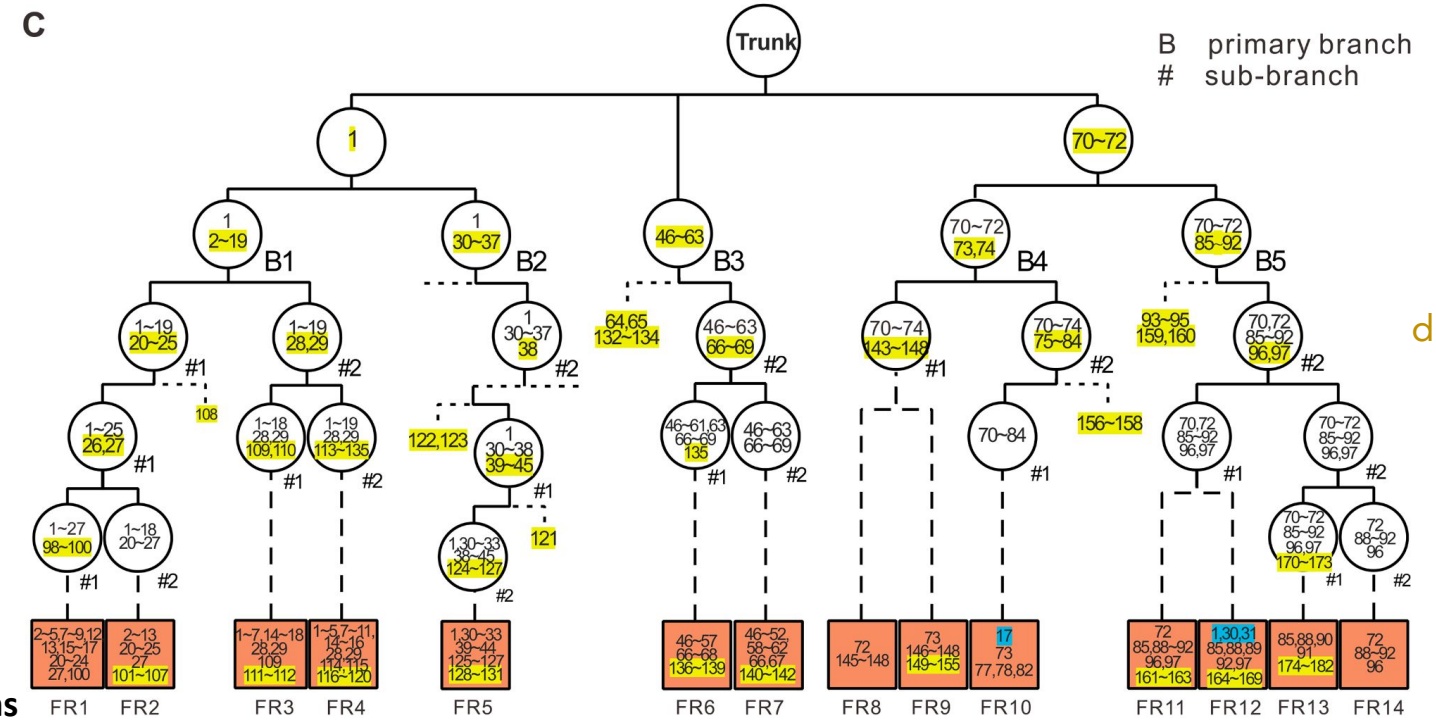




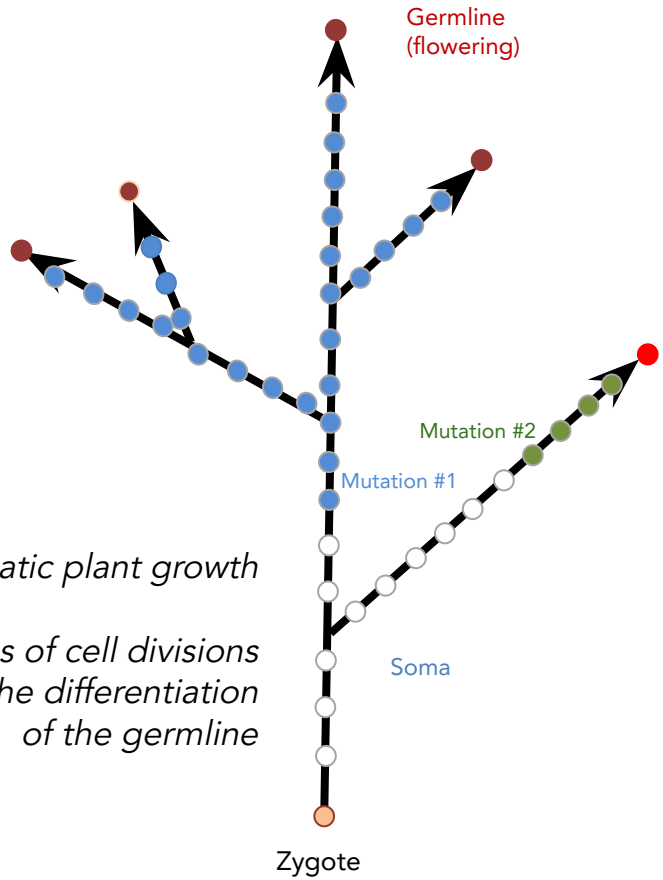
71% of inherited mutations

Mutations discovered within the tree

Mutations recovered in the progeny (14 seeds)

modified from Wang et al. 2019 PLoS Biology

Summary: plant mutations (up to now)



Somatic plant growth

millions of cell divisions before the differentiation of the germline

A mutation happens in a population of cells (a meristem): a methodological challenge

It requires to adapt methods initially developed for cancer genomics

Mutation accumulate along plant growth

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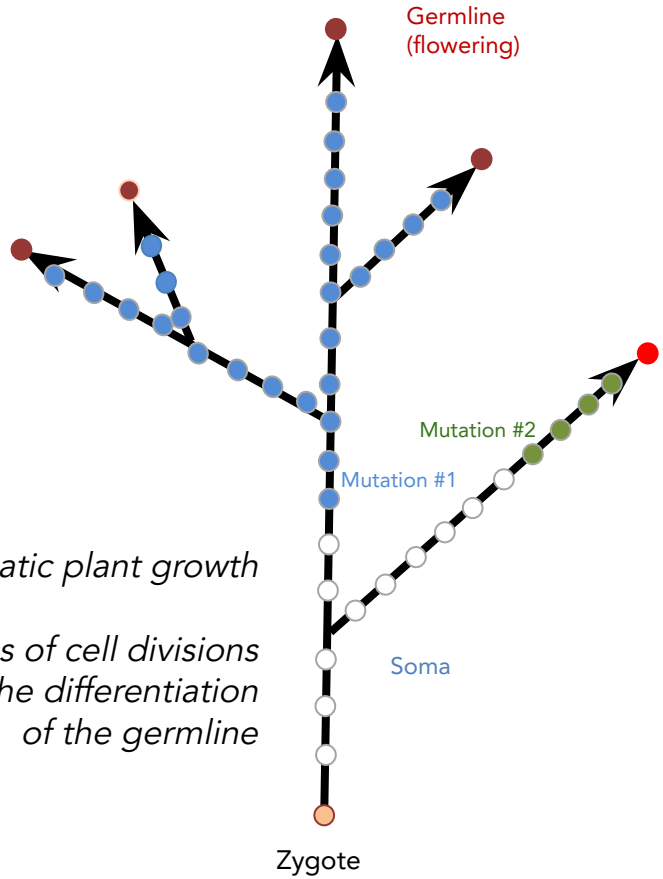
To finish: three recent work in plants changing our views about plant mutations.



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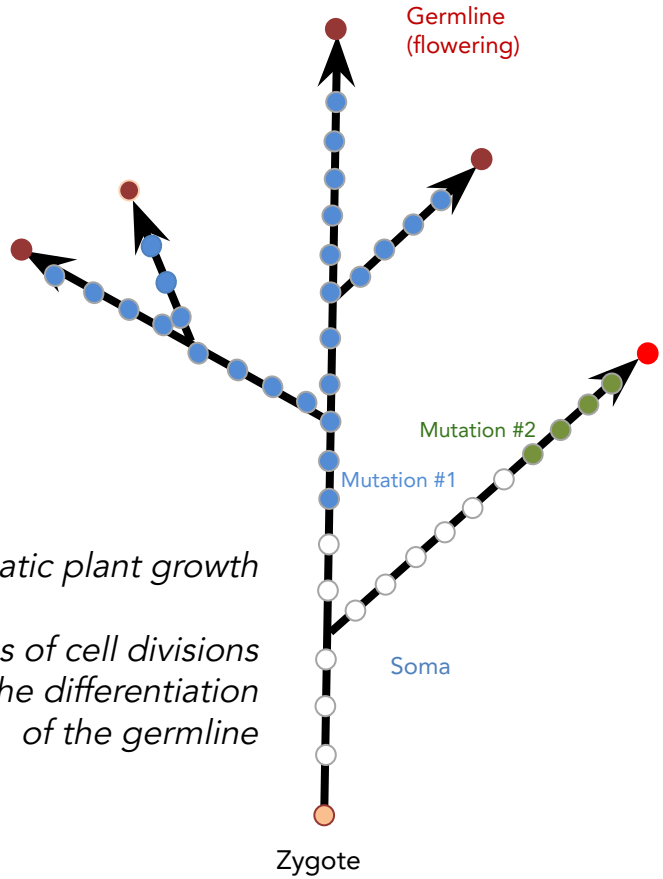

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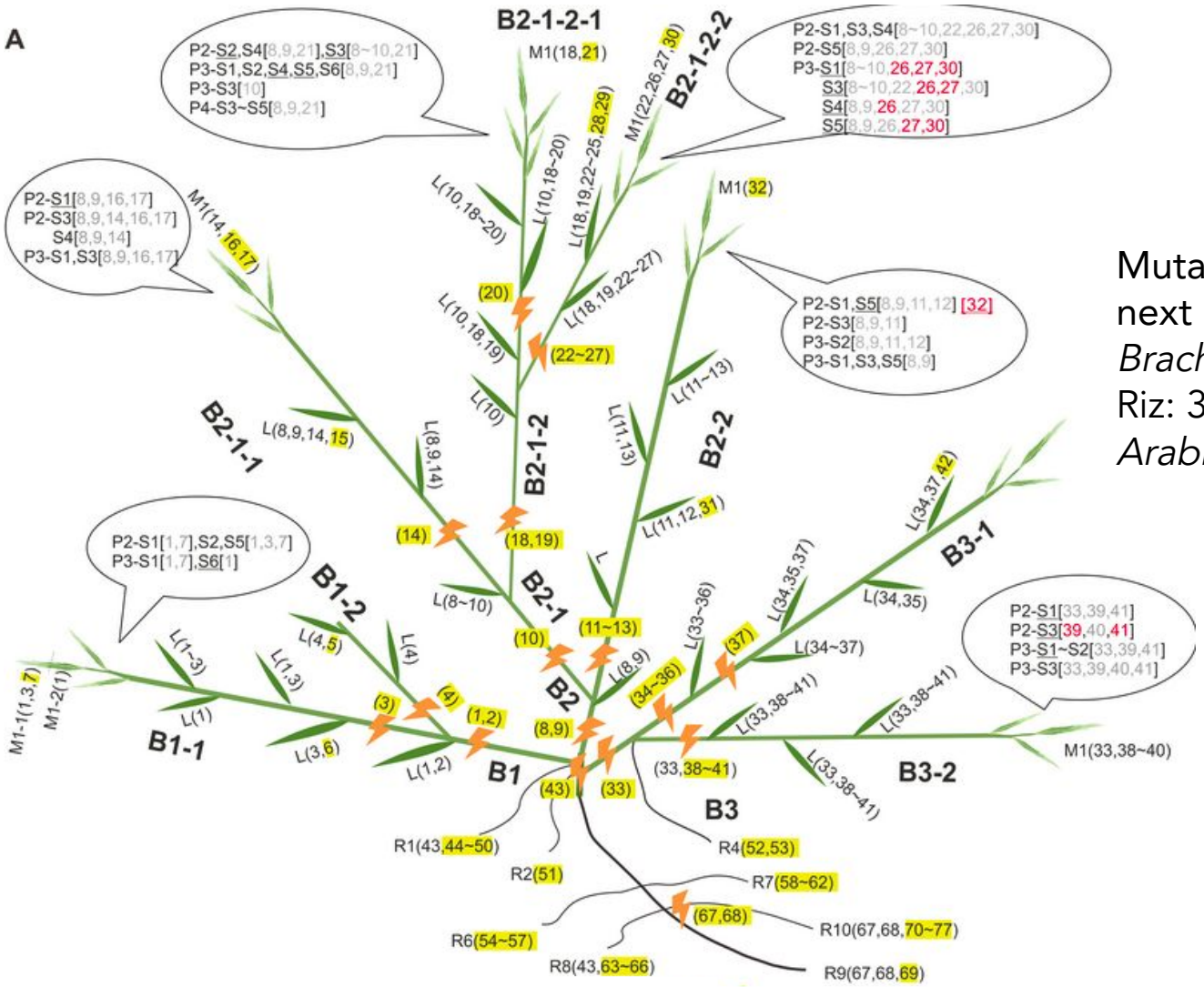
A very low proportion of heritable mutation rates in annuals?

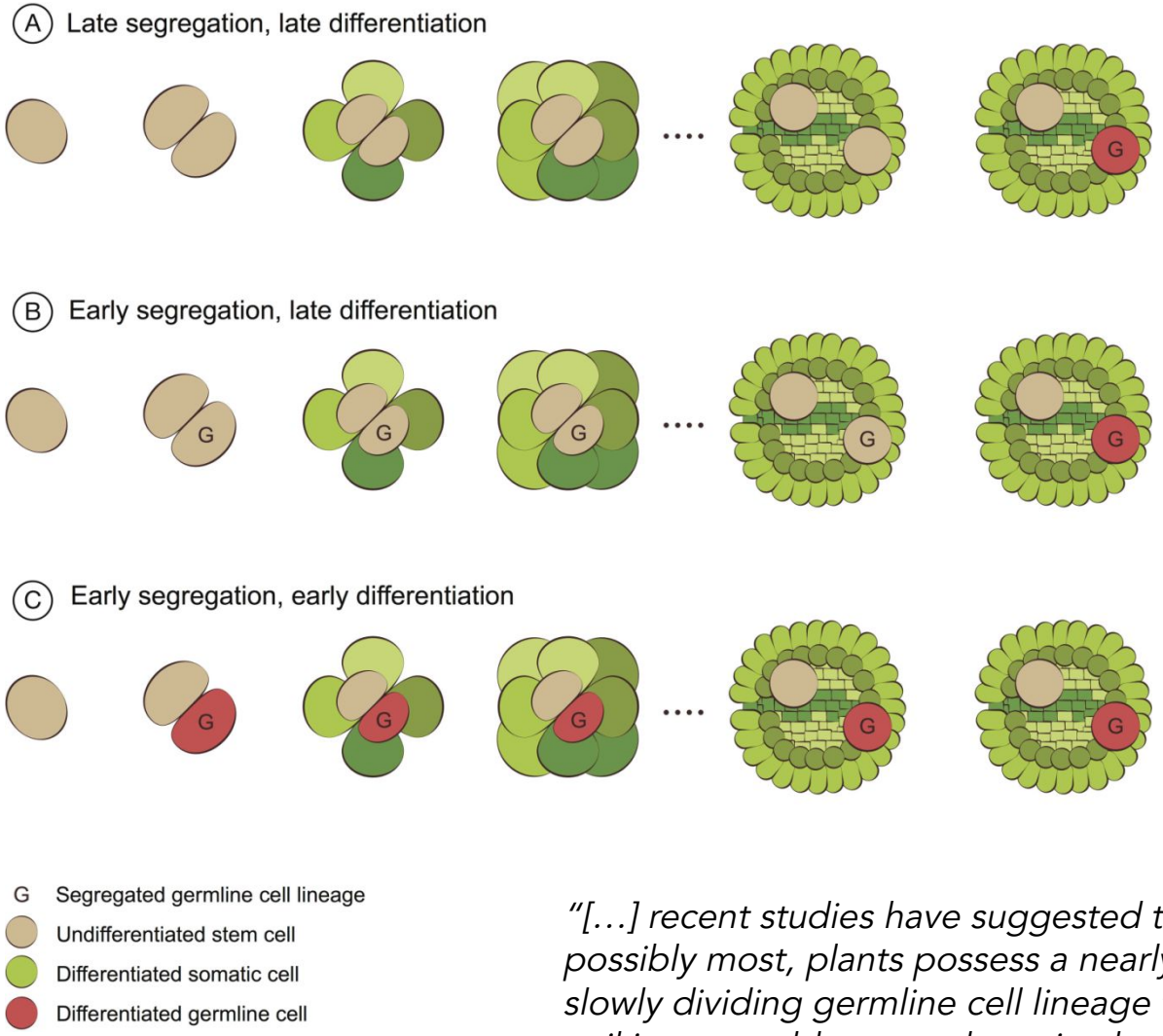


Mutations transmitted to the next generation:
Brachypodium: 10/159 (6.3%)
Riz: 3/100 (3.0%)
Arabidopsis: 1/58 (1.7%)

A main difference between annuals and perennials?

Wang et al. 2019 PLoS Biology

Which proportion of plants deviate from the Weissmann's theory?



"[…] recent studies have suggested that some, and possibly most, plants possess a nearly-segregating and slowly dividing germline cell lineage that bears a striking resemblance to the animal germline"

Robert Lanfear, 2018 PLoS Biology

Summary: plant mutations (up to now)

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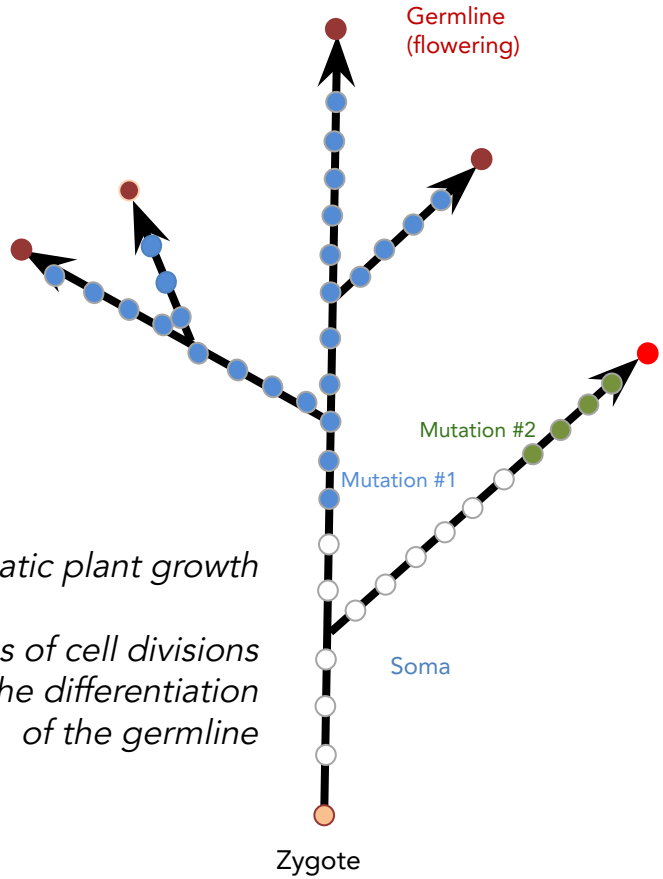

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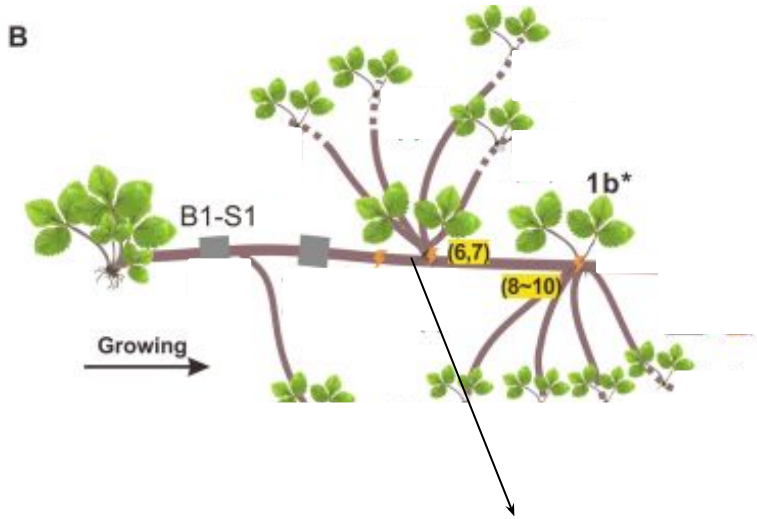
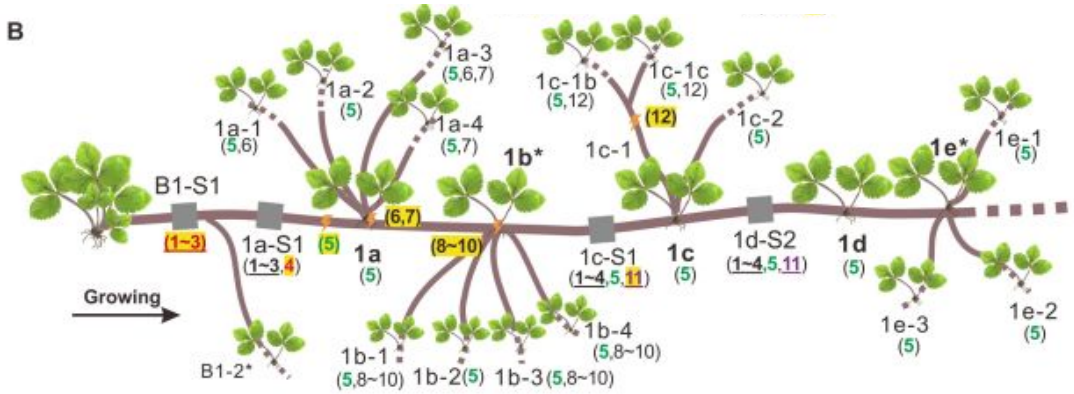
Mutations accumulated along growth? Which growth?



Runners (« stolons »)
= Vegetative propagation



Two different cell lineages in runners? Some somatic mutations that are never transmitted to the clonal plants? A way to keep mutations under control?

Wang et al. 2019 PLoS Biology

Summary: plant mutations (up to now)

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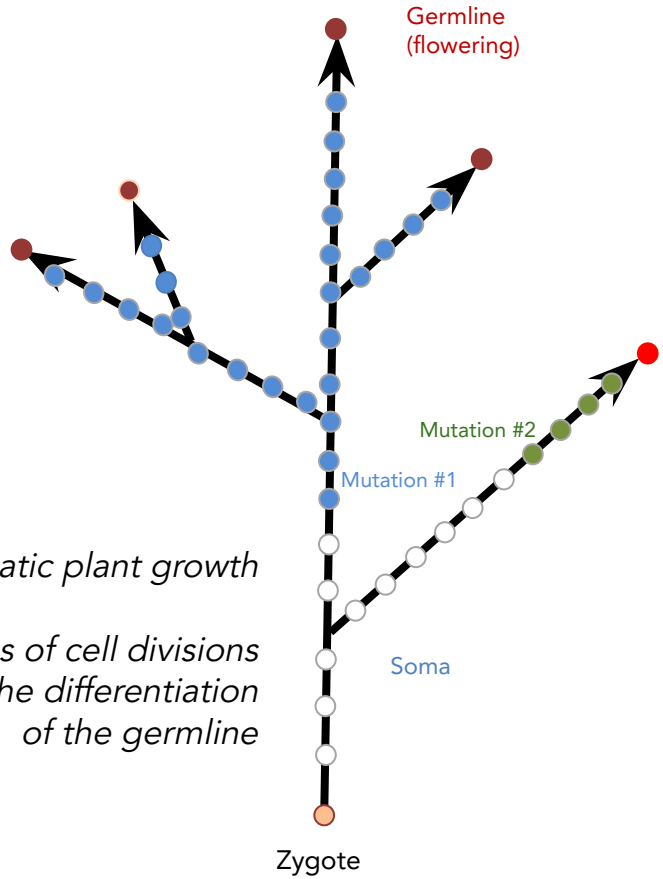

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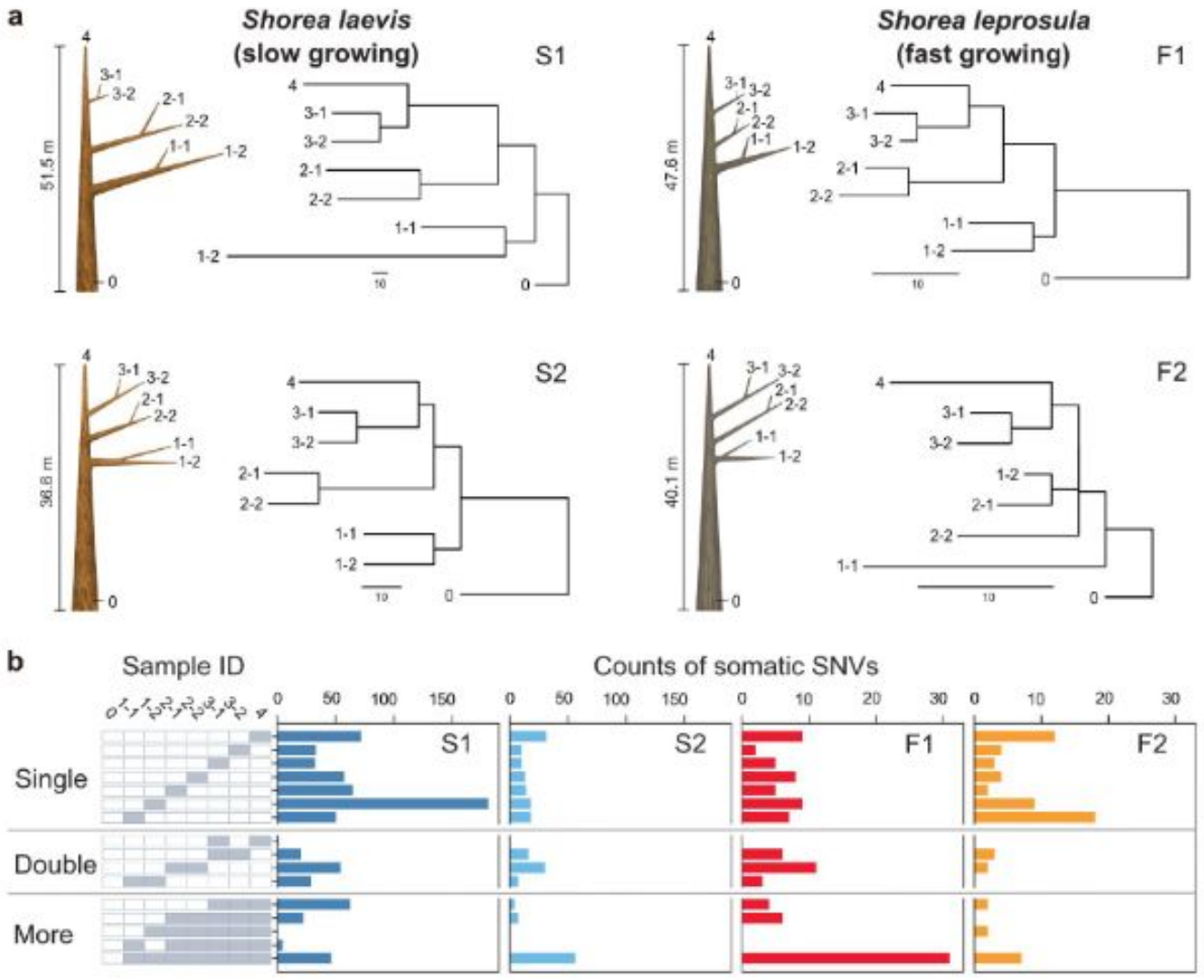
Mutation accumulate along growth: an effect of the cell divisions or the DNA repair?

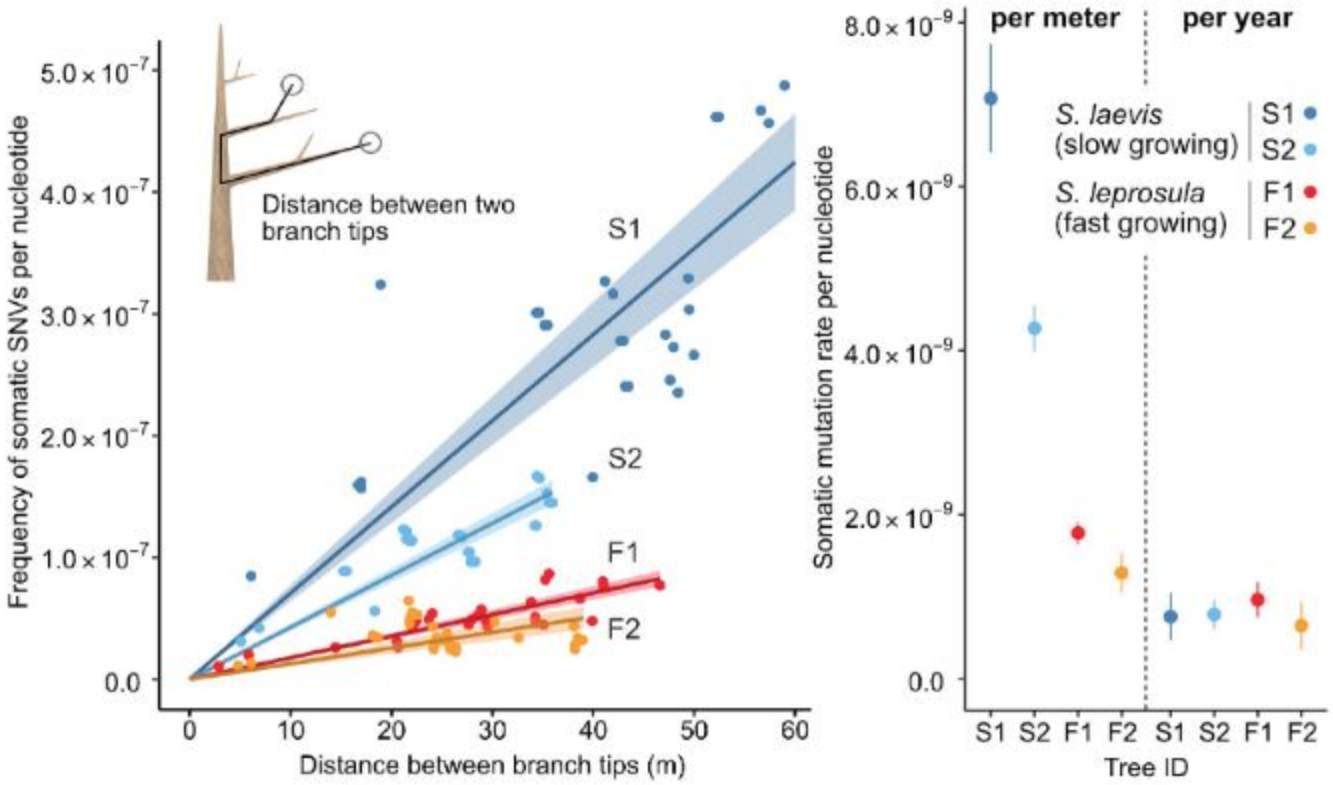
Detection of mutations

256 years old trees on average | **66 years old trees on average**



Satake et al. 2023, eLife

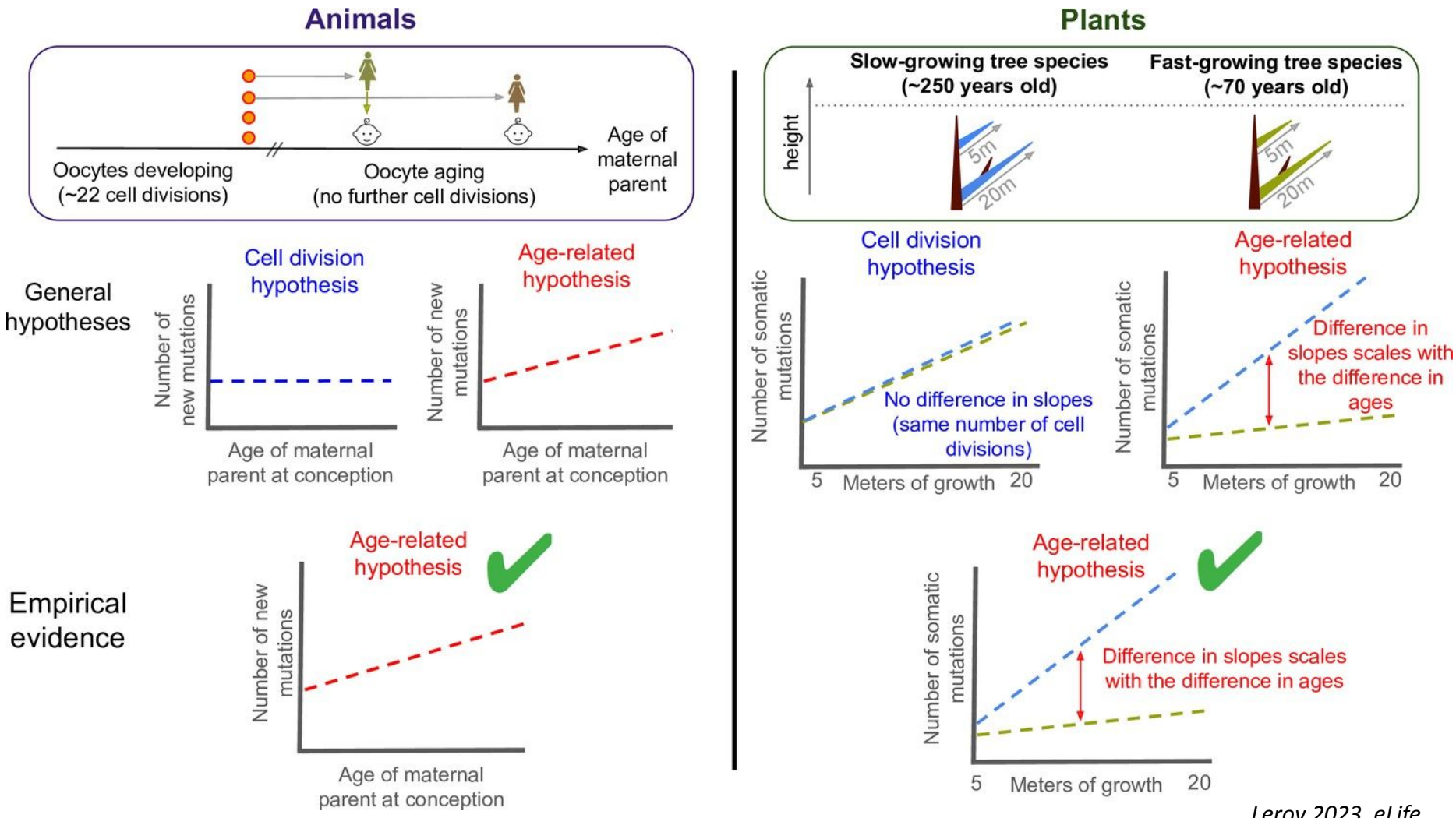
Mutation accumulate along growth: an effect of the cell divisions or the DNA repair?



The slow-growing species obtained 3.7 times more mutations per meter than the fast-growing tree, after considering the physical distance between branch tips

Satake et al. 2023, eLife

Age seem to be the main factor explaining rates, an interesting parallel with animals

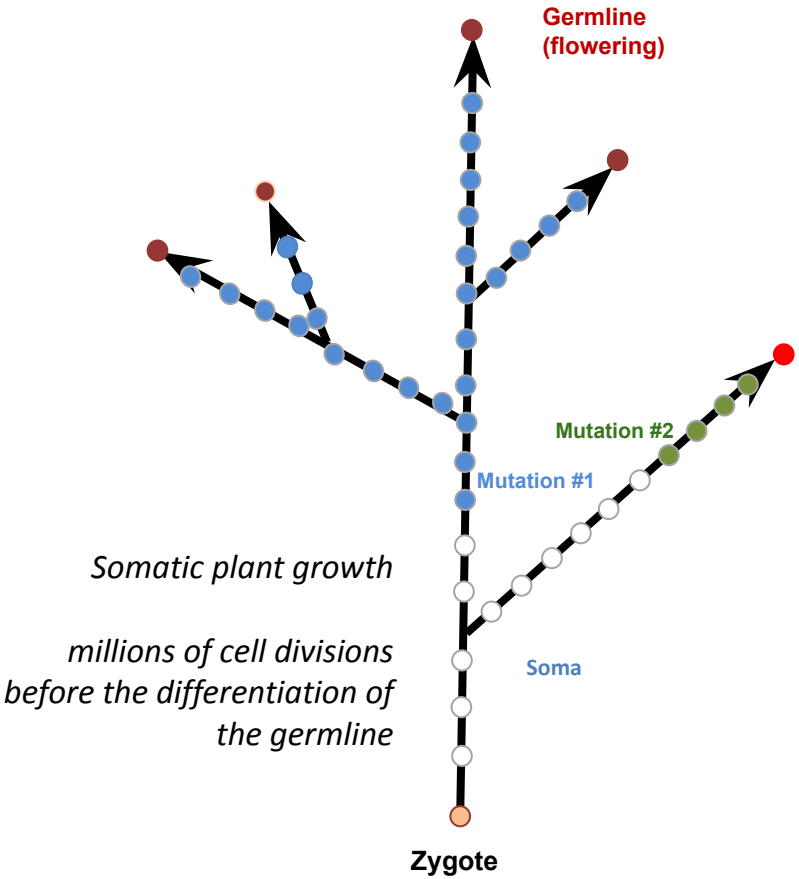


Leroy 2023, eLife

Recent evidences suggest that mutation accumulates with age rather than the number of cell divisions in both plants and animals, suggesting largely conserved mutational processes.

Summary: plant mutations (up to now)

To finish, I summarize three recent work in plants changing our views about plant mutations.



A mutation happens in a population of cells (a meristem): a methodological challenge

It requires to adapt methods initially developed for cancer genomics

→ **To what extent is the frequency of the somatic mutation matters for plant mutations?**

Mutation accumulate along tree growth

→ **Does this vary depending on the tissues? Are mutations generated by DNA replication or DNA repair errors?**

Somatic mutation can be passed to the progeny in plants

→ **Does this apply to all plants?**

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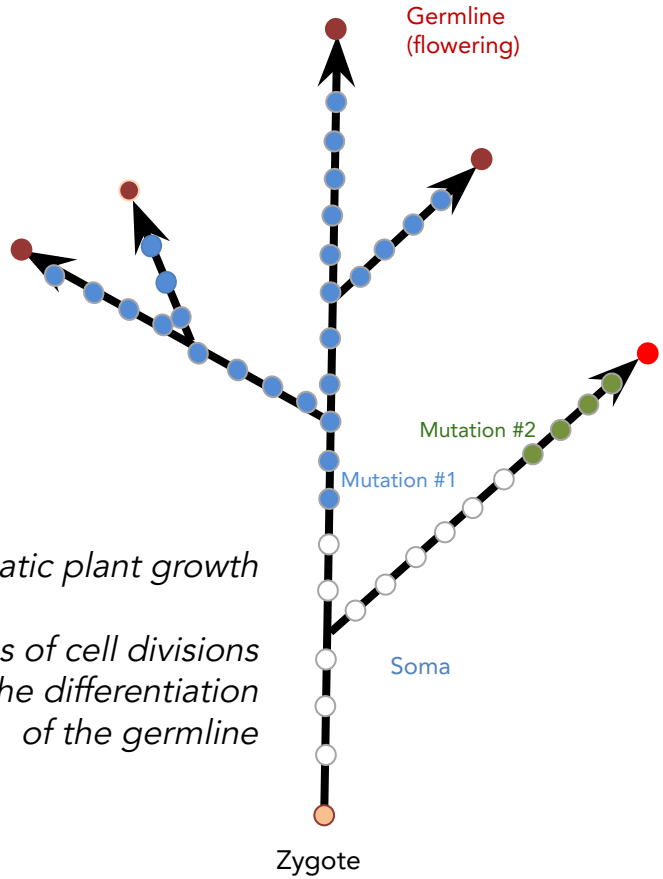

Somatic plant growth

millions of cell divisions before the differentiation of the germline

A mutation happens in a population of cells (a meristem): a methodological challenge

It requires to adapt methods initially developed for cancer genomics

→ To what extent is the frequency of the somatic mutation matters for plant mutations?

Mutation accumulate along plant growth

→ Does this vary depending on the tissues? Are mutations generated by DNA replication or DNA repair errors?

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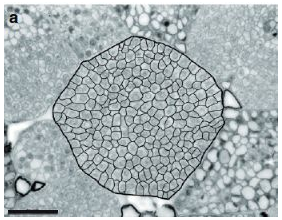
→ Does this apply to all plants?

Can we (really) identify mutations at low allele frequency?

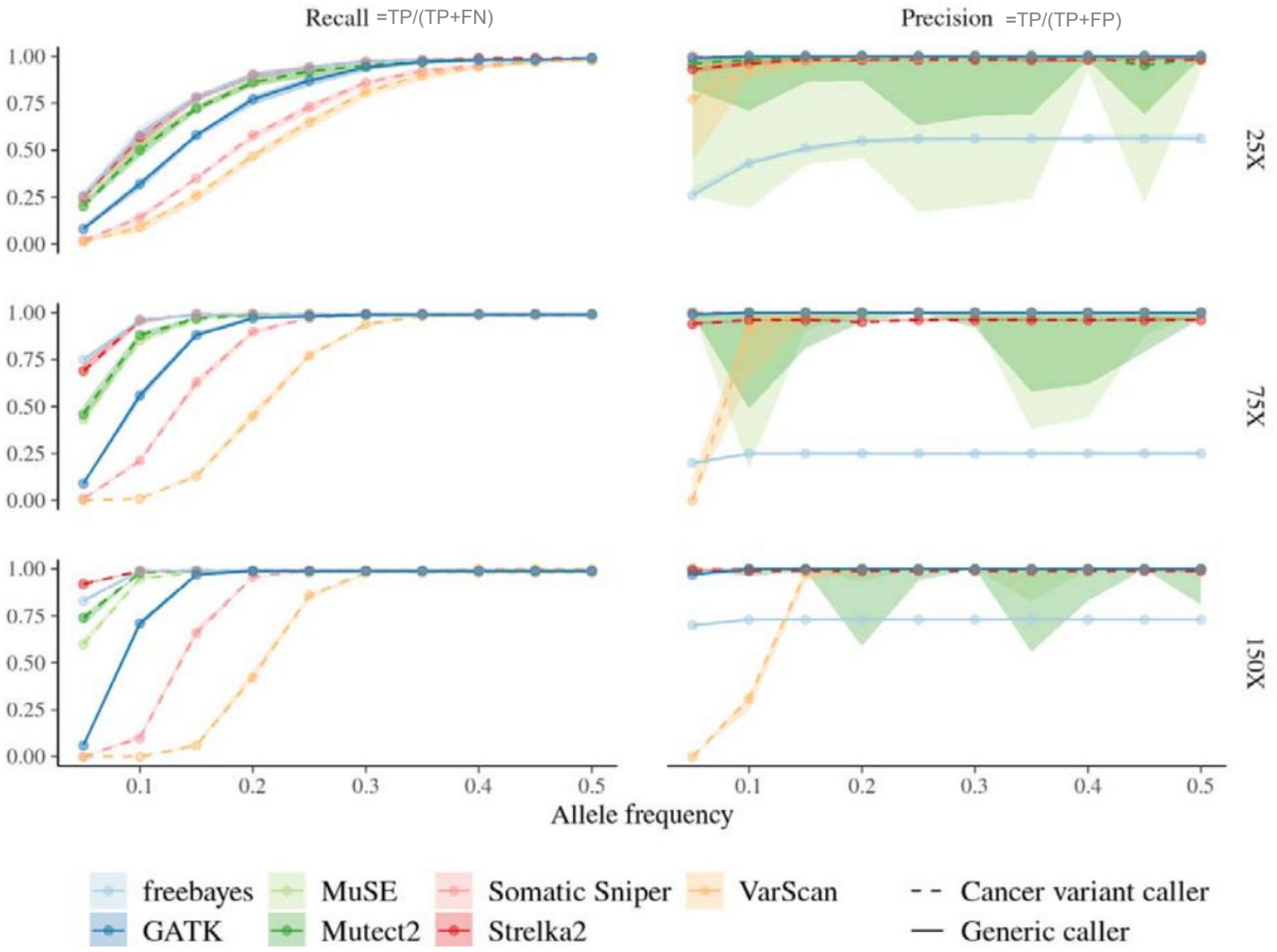
Simulation study (depth of coverage/ frequency of mutation, different callers)



Sylvain Schmitt
Postdoc
INRAE Kourou (2021-2023)
now researcher at CIRAD

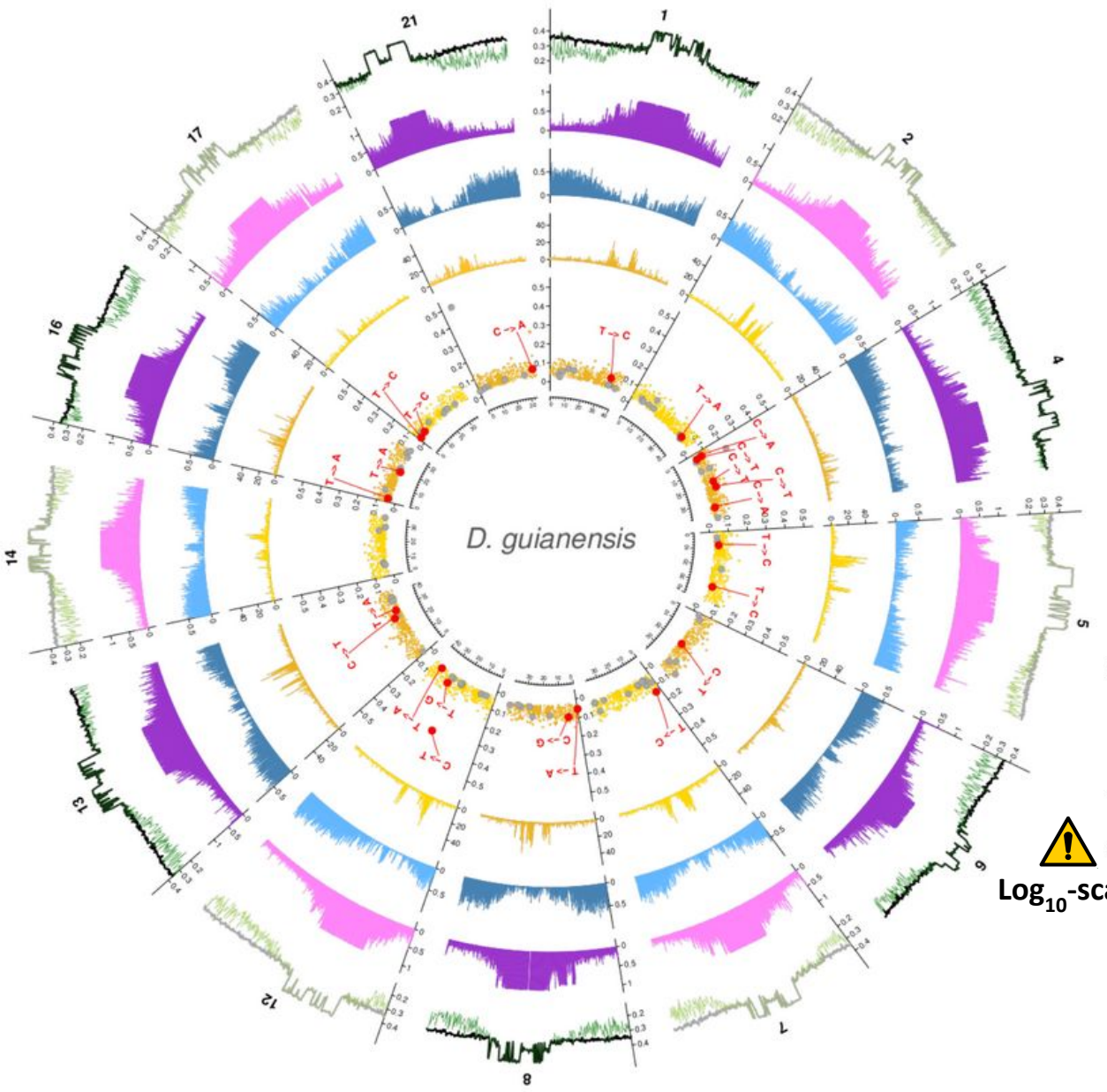
Myriam Heuertz

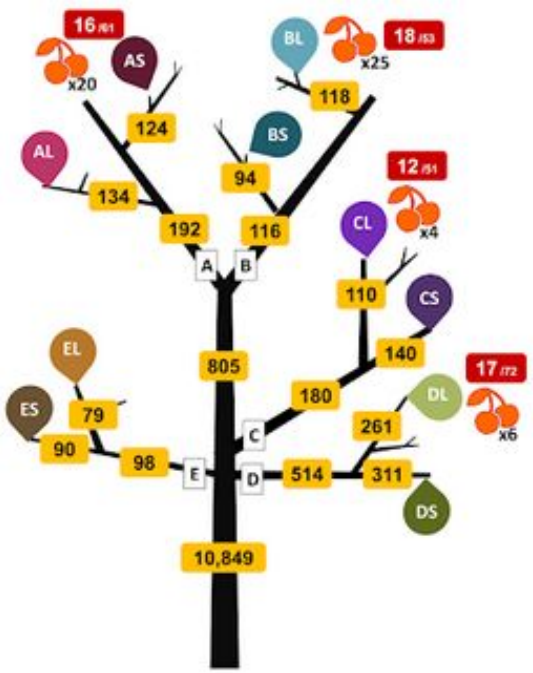
Niklas Tysklind

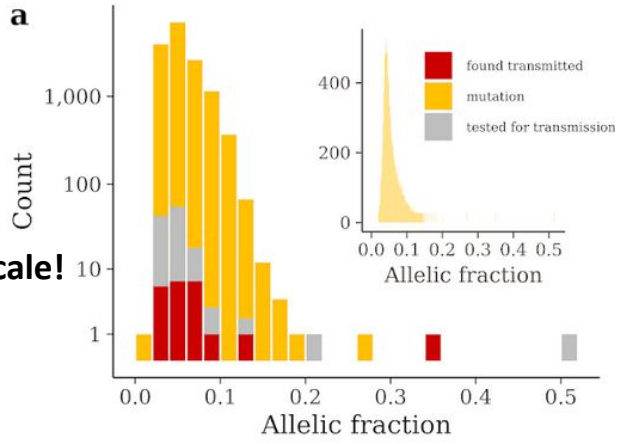


Schmitt et al. 2022, PCJ

So if it is theoretically possible to identify low freq mutations, at which allele frequency new mutations are observed?







Log$_{10}$-scale!

Schmitt et al. 2023, BioRxiv

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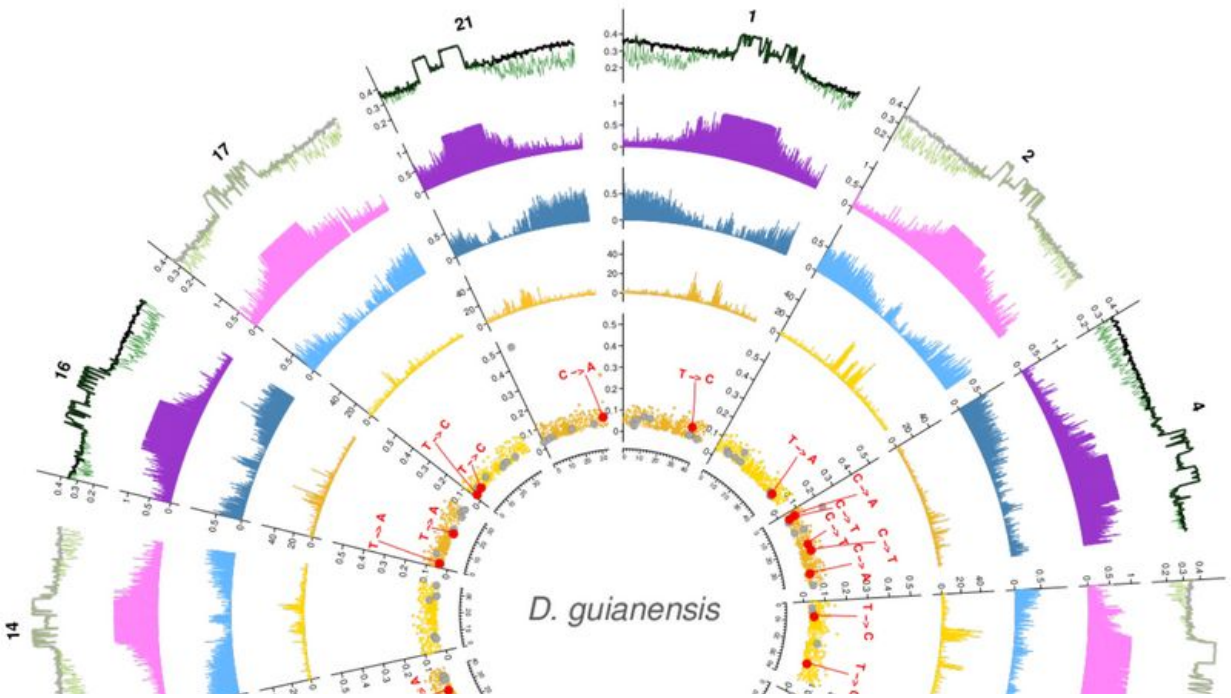
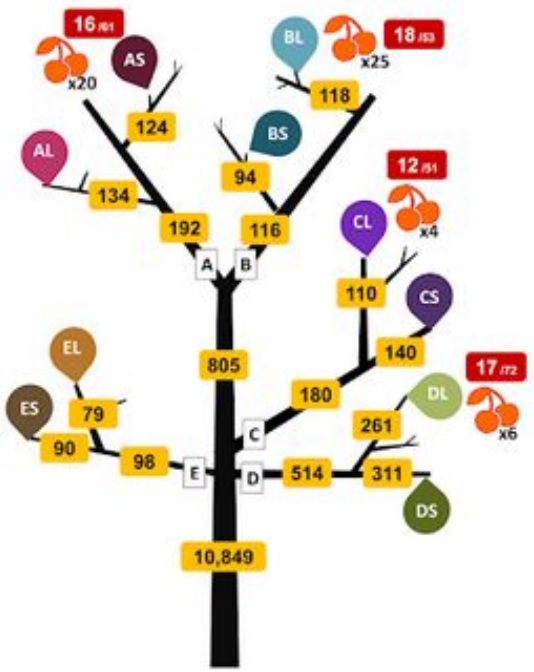
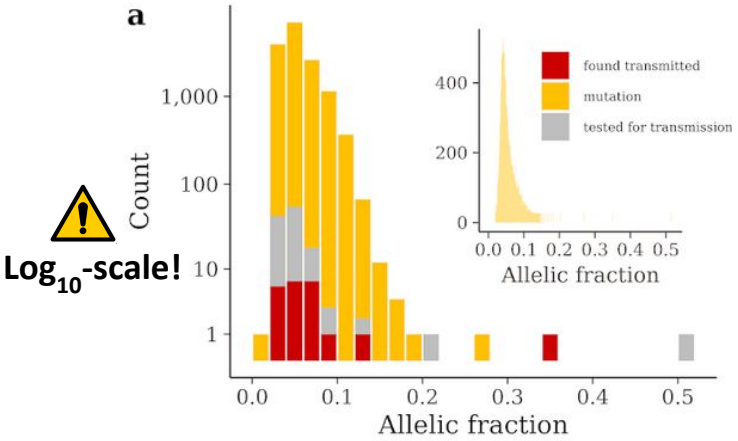




The vast majority of de novo plant mutations are at low allele frequency within the plant and are therefore difficult to detect, but they can be evolutionary important, since these mutations can also be transmitted to the next generation!



Schmitt et al. 2023, BioRxiv

Existing knowledge on plant somatic mutations (almost all)

Detection of plant somatic mutations:

- Somatic mutations are indeed produced along growth (widely supported empirically)
- Cancer-derived methods are more robust to identify these variants
- Almost nothing is known about plant mutation rates and spectra

Inheritance of plant somatic mutations:

- Some species (e.g. oak, peach trees) found considerable support for the inheritance of somatic mutations…
- … and are therefore expected to be a significant proportion of the heritable mutations…
- … but this is probably not true for all species, especially annual plant species (similarities with the early segregation of the animal germline?)

In plants, there is increasing evidence that the relationship between growth, aging and heritable mutation rate is much more complex than previously thought

Take home message

Mutation is the engine of evolution and therefore represents a crucial evolutionary process to study in biology

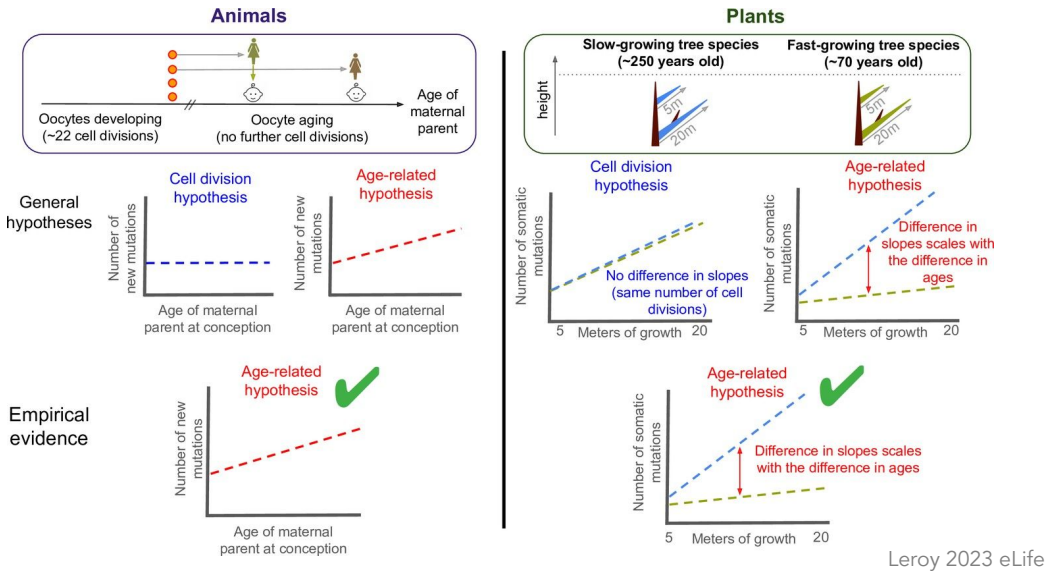
The per-generation heritable mutation rate: importance for genetic diversity ($4N_e\mu$) and divergence (molecular clock)

Albeit understudied from an evolutionary perspective, the study of mutational processes is essential. **Mutation is as complex as any other evolutionary forces!**

Mutation is random, but the probability for such an event is variable depending on the environmental (mutagens) and genomic contexts (spectra)

Growing evidence that mutation accumulates with age rather than with the number of cell divisions (DNA repair vs. replication)

Despite limiting research in plants, recent evidence suggest that mutational biases could be conserved between animals and plants



Leroy 2023 eLife

Especially dynamic field: most of the knowledge presented during this 2-hour course is less than 10 years old.

Mutations in animals and plants: an introduction

Ron and Joyce Bond
(UK's (World's?) oldest living married couple)

« The Major Oak », Sherwood Forest, Nottinghamshire, England (800-1,000 years old, UK's most visited tree)

Thibault Leroy

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