

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)



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Tracking domesticated and wild bees through... DNA traces



GENETIC DIVERSITY
OF HONEY BEES
USED BY BEEKEEPERS



ADAPTATION OF
HONEY BEES
(PARASITES, CLIMATE)



EFFICIENCY OF QUEEN
FERTILIZATION AND
GENETIC GAIN



TRACEABILITY OF
BEEHIVE PRODUCTS
(HONEY, ROYAL JELLY,
BEESWAX, ...)



COMPARISONS OF
GENOMES OF WILD AND
DOMESTICATED BEES



QUALITY OF THE
POLLINATION SERVICE
PROVIDED BY BEES

Round table discussion

What you can tell me
about mutation?



Round table discussion

What you can tell me about mutation?

Hummm, I am
sure you don't
know what is the
mutation rate in
human?



Round table discussion

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And you, Mr.
Know-It-All, do
you know if all
mutations are
equally frequent?

Before to start... a few 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, inversion or translocation, ...)
- Animal & plant species

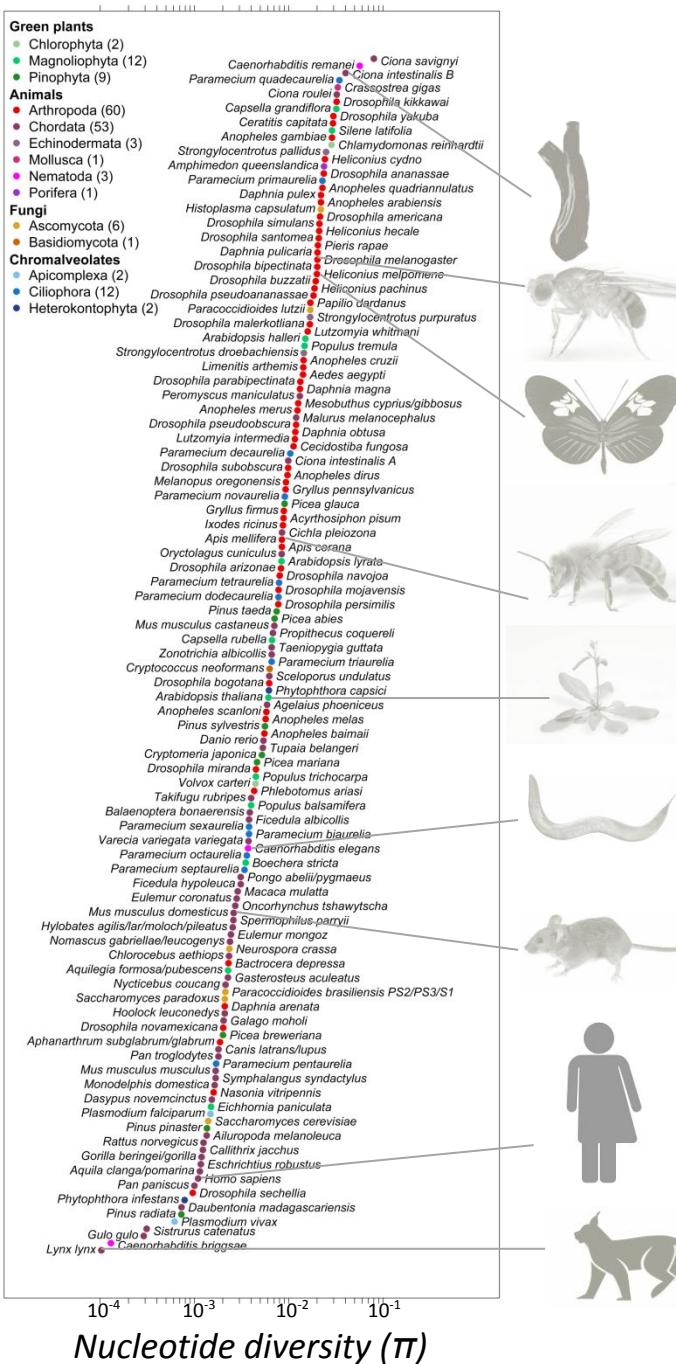


Why mutation rate (μ) is a so important parameter in biology?

Estimating the levels of genetic diversity across the tree of life

1:AAATACCAACAAC | 1 difference
 2:AAATACCA**T**CAAC | 1 difference
 3:AAATACCA**T**CAAG
 4:AAATACCA**T**CAAC
 5:AAATACCA**TC**GAC

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



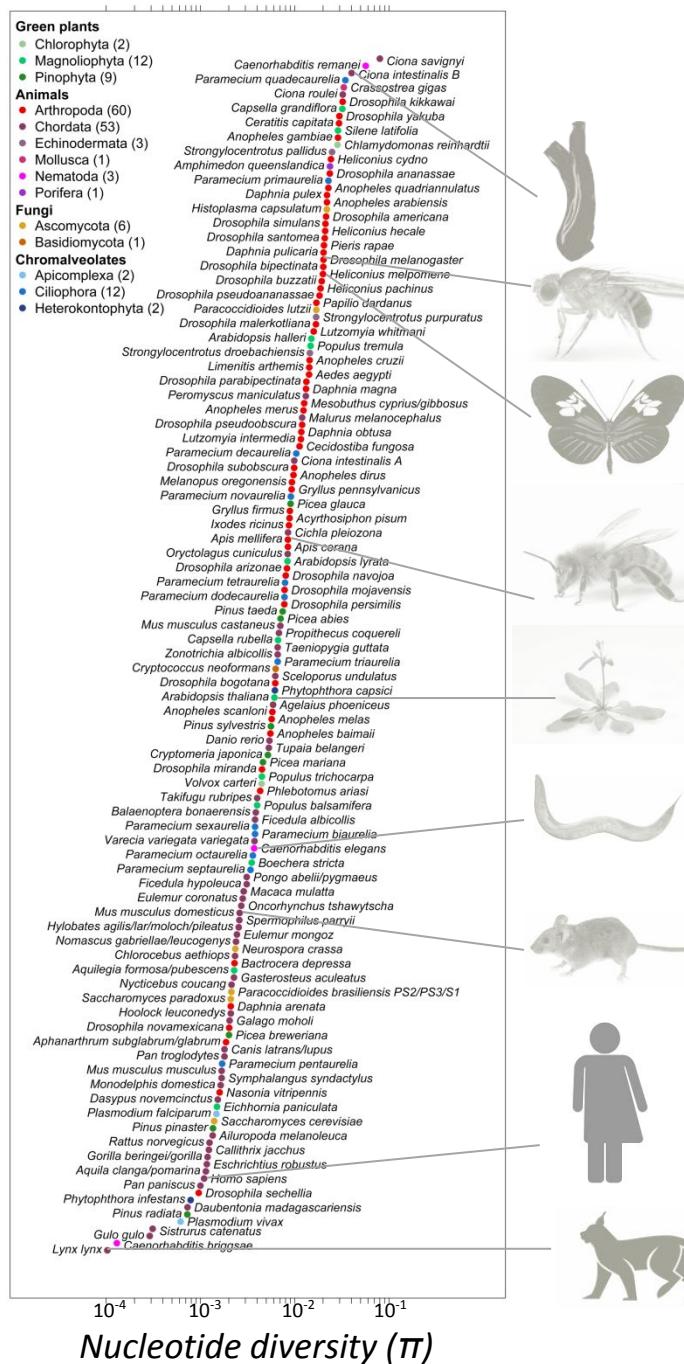
Leffler et al. Plos Biol 2012

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Genetic diversity within a population

(Standing genetic variation)

At mutation-drift equilibrium:

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

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

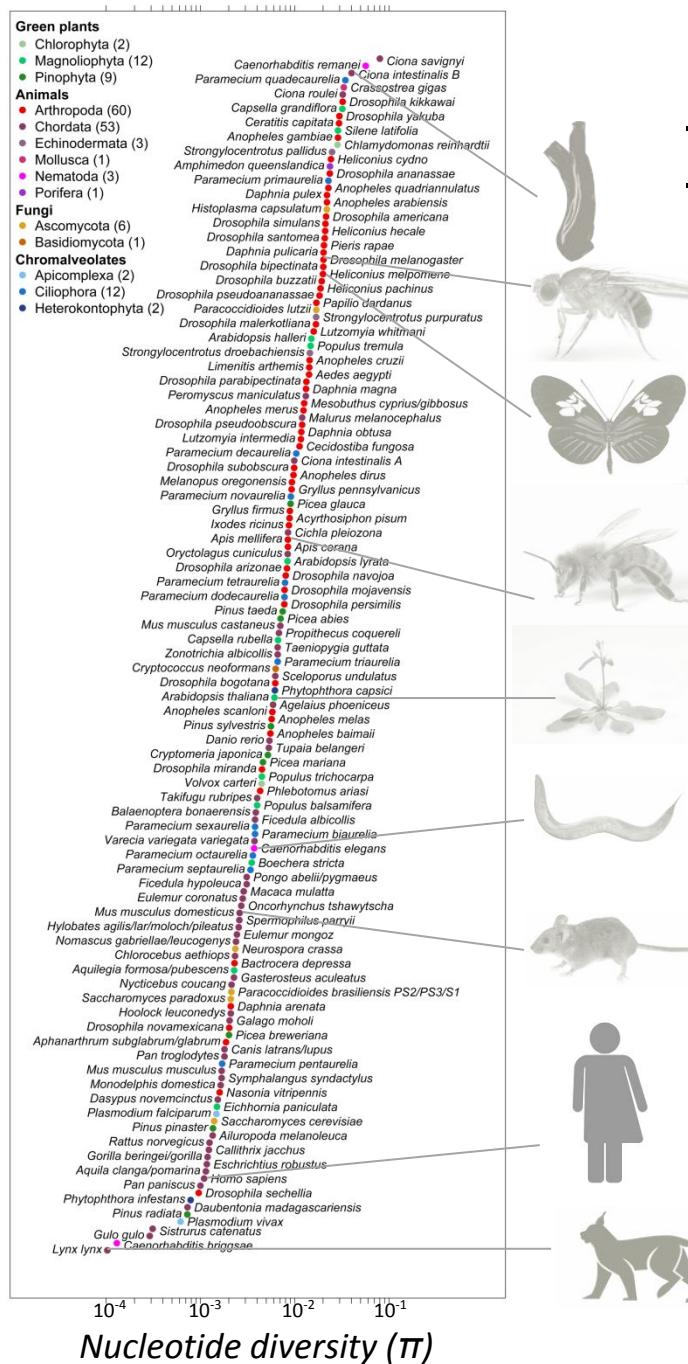
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Leffler et al. Plos Biol 2012



Genetic diversity within a population

(Standing genetic variation)

At mutation-drift equilibrium:

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

Divergence between species

Following the neutral theory:

$$\text{Rate of neutral substitutions} = 2 N_e * \mu * \frac{1}{2 N_e} = \mu$$

Molecular clock
(Kimura, 1968)



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

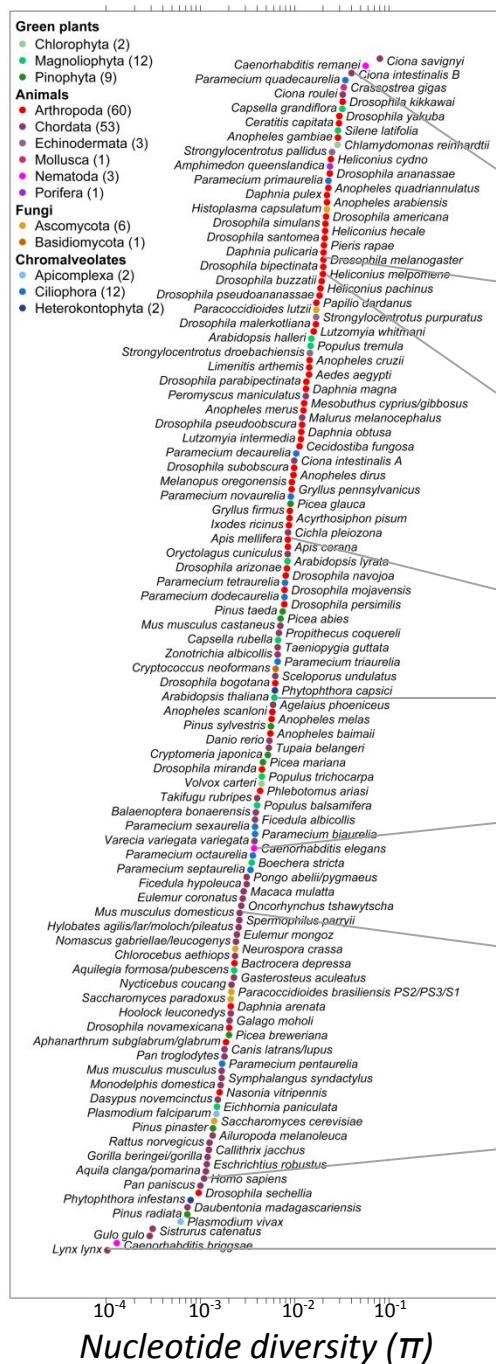
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π the average number of nucleotide differences per site between pairs of sequences

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



Nucleotide diversity (π)

Genetic diversity within a population

(Standing genetic variation)

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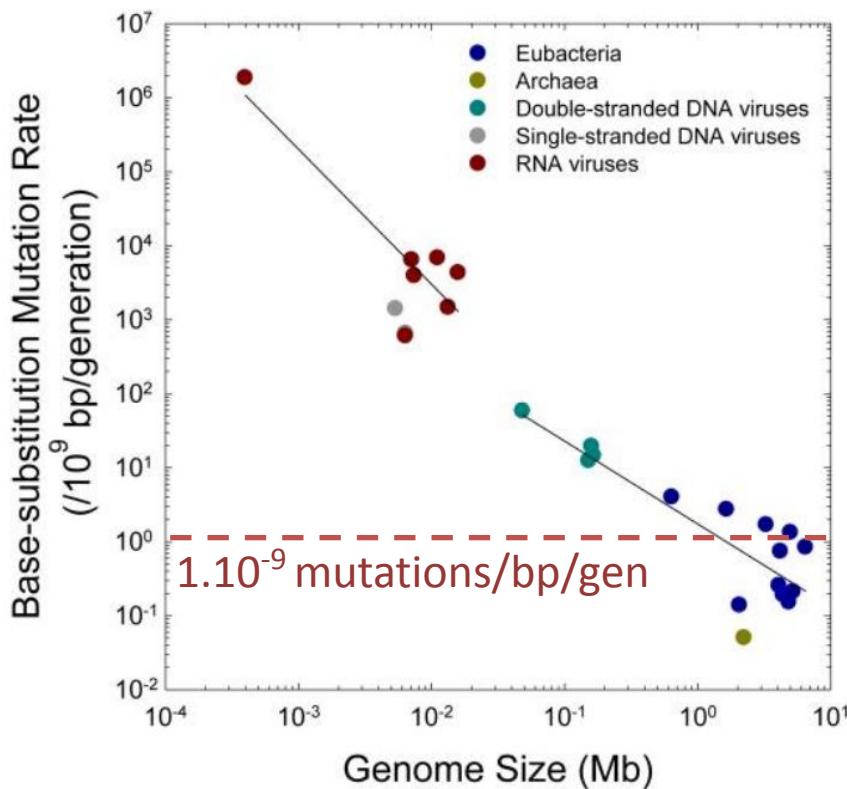
Molecular clock
(Kimura, 1968)



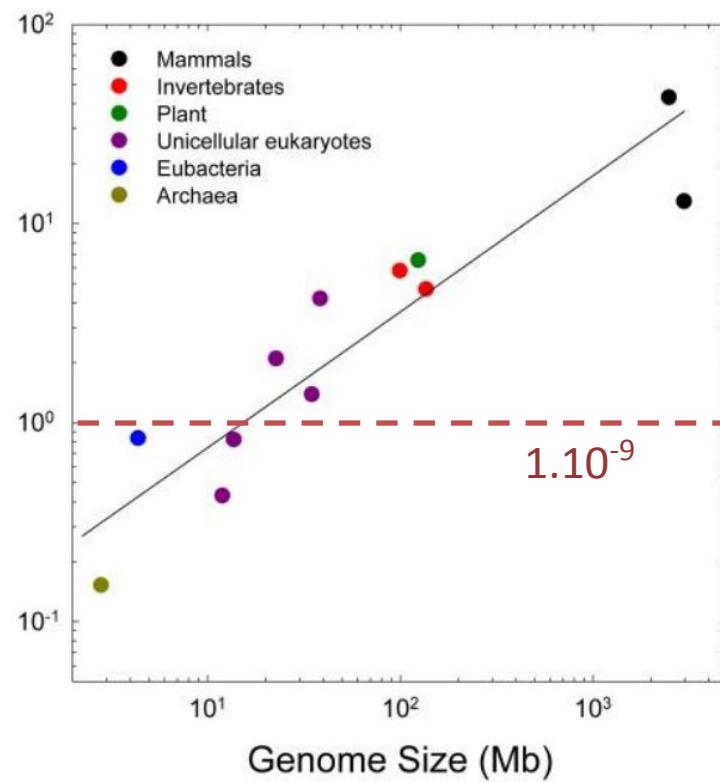
The conversion

Mutation rate (μ) is variable among species

Viruses & bacteria



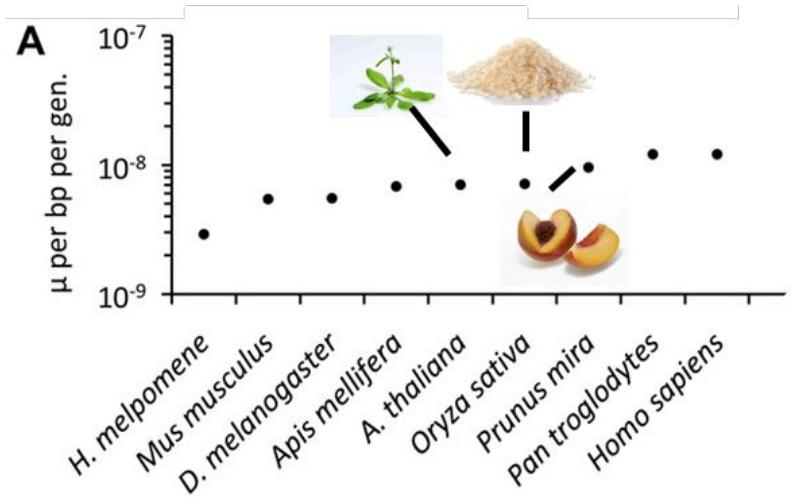
(Bacteria &) Eukaryotes



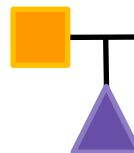
Lynch, 2010 Trends Genet

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

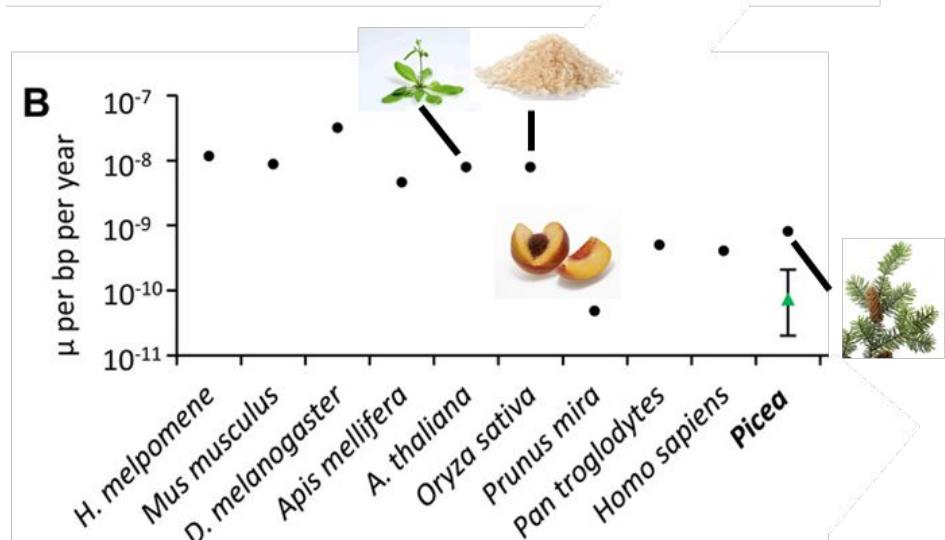
Mutation rate (μ) is variable among species



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."

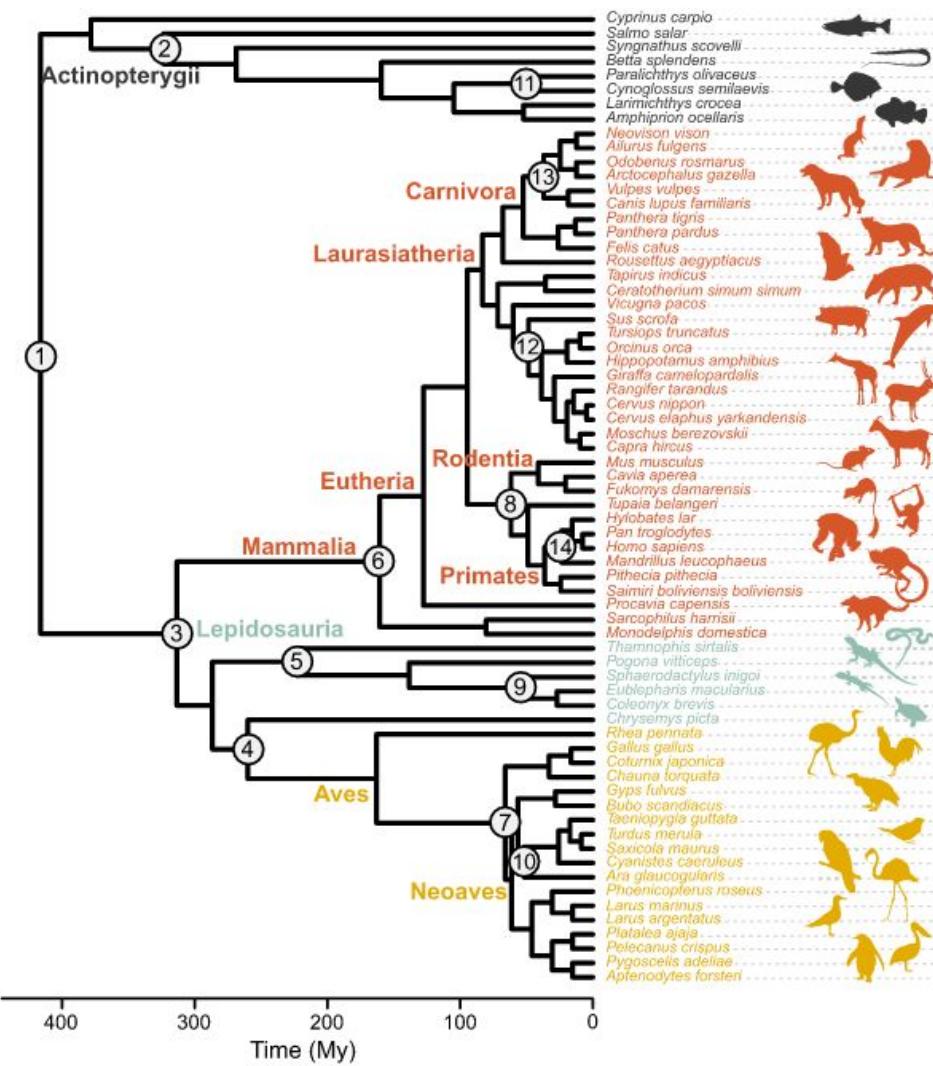
Modified from Hanlon *et al.*
2019 Evolution Letters

Mutation rate (μ) is variable among species

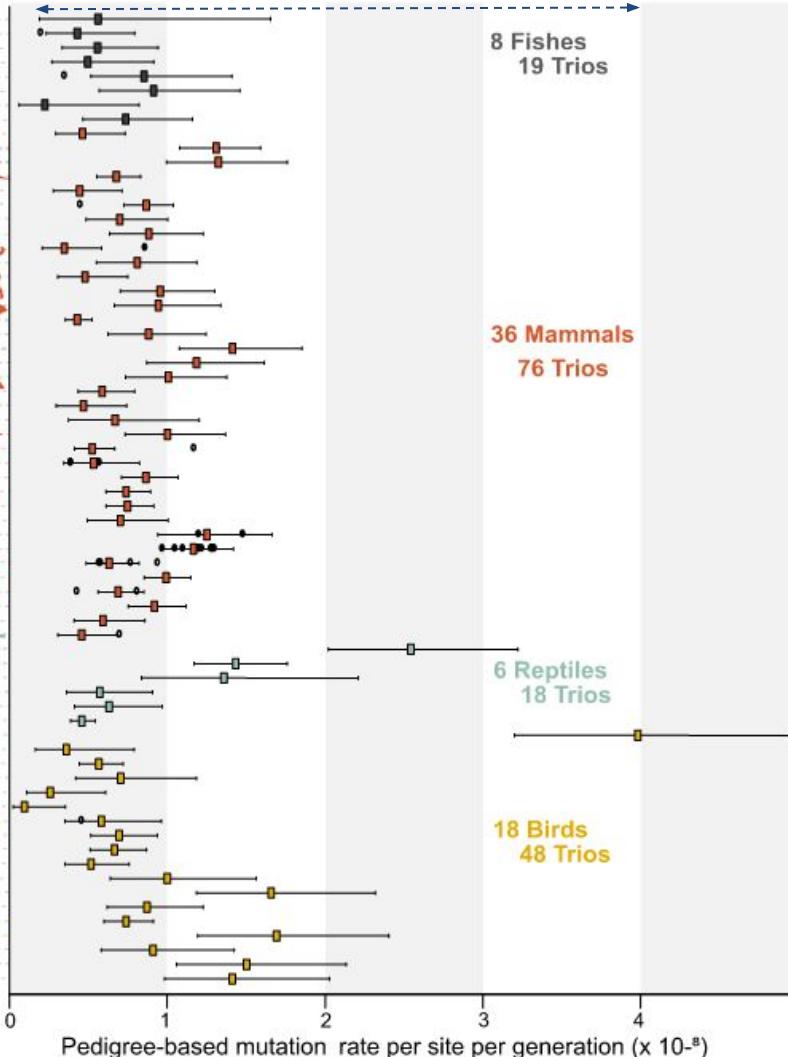
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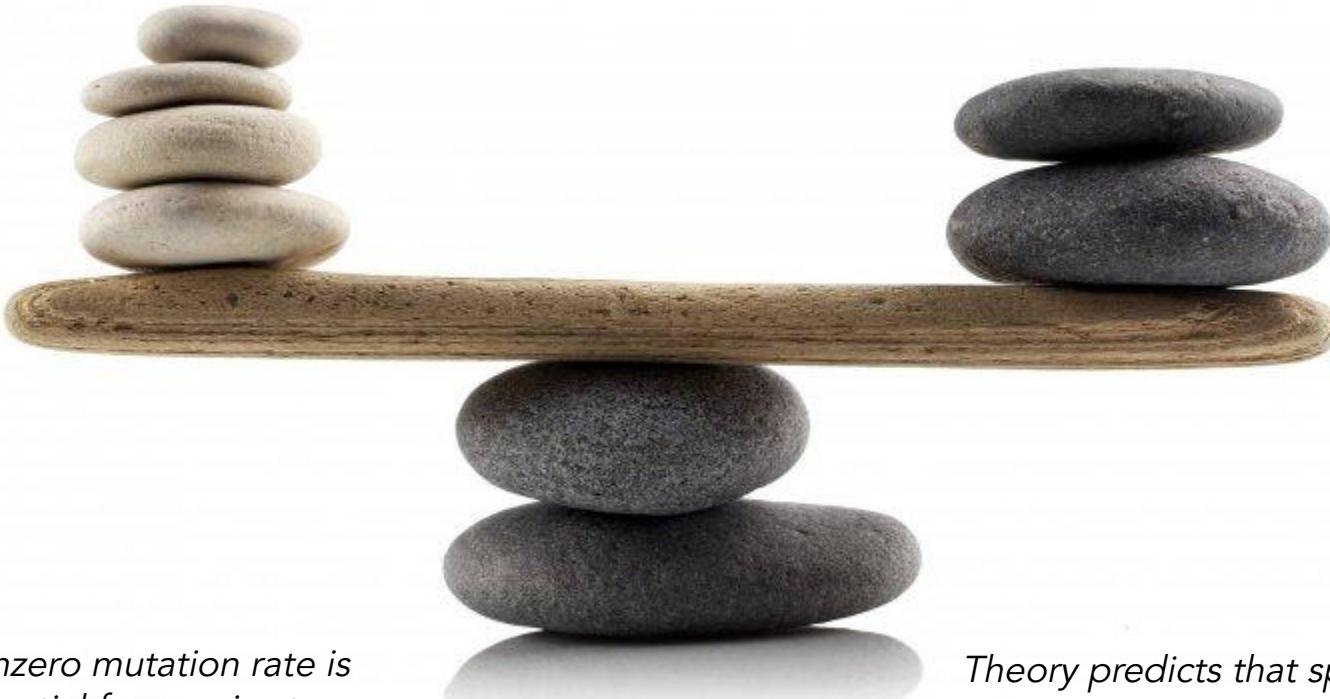


40-fold difference!



Why do mutation rates vary among species?

Evolvability
(some new adaptive mutations)



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

Mutational burden
(Deleterious mutations)

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)

?



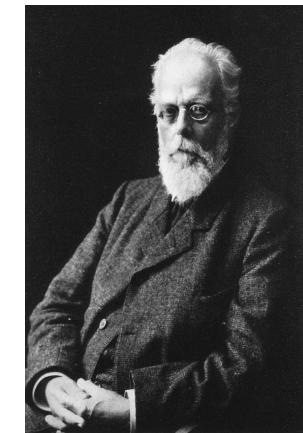
« The Major Oak », Sherwood Forest, Nottinghamshire,
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?

August Weismann's theory: Germline vs. soma

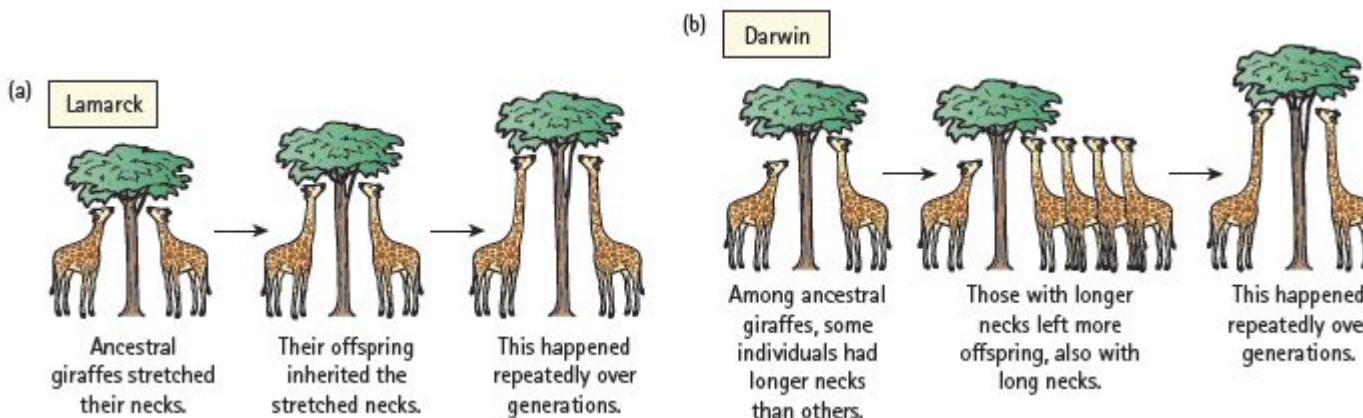
One of the greatest 19th century evolutionary biologist

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



August Weismann
(1834-1914)

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



Theory of natural selection (Darwin, 1859)

Theory of inheritance (Weismann, 1892)

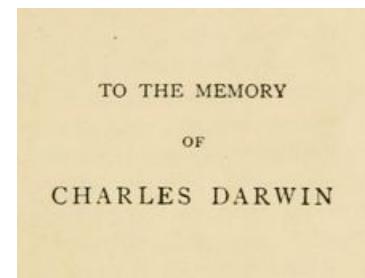
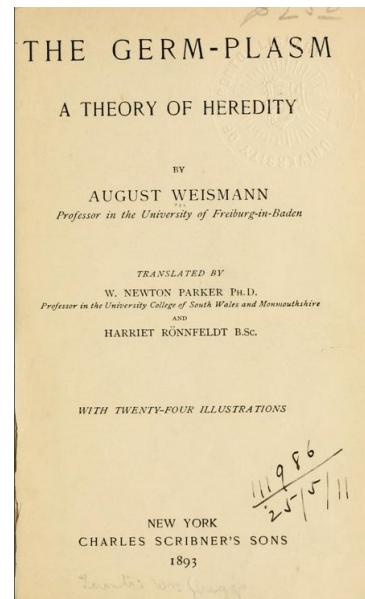
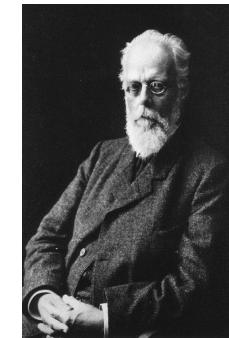
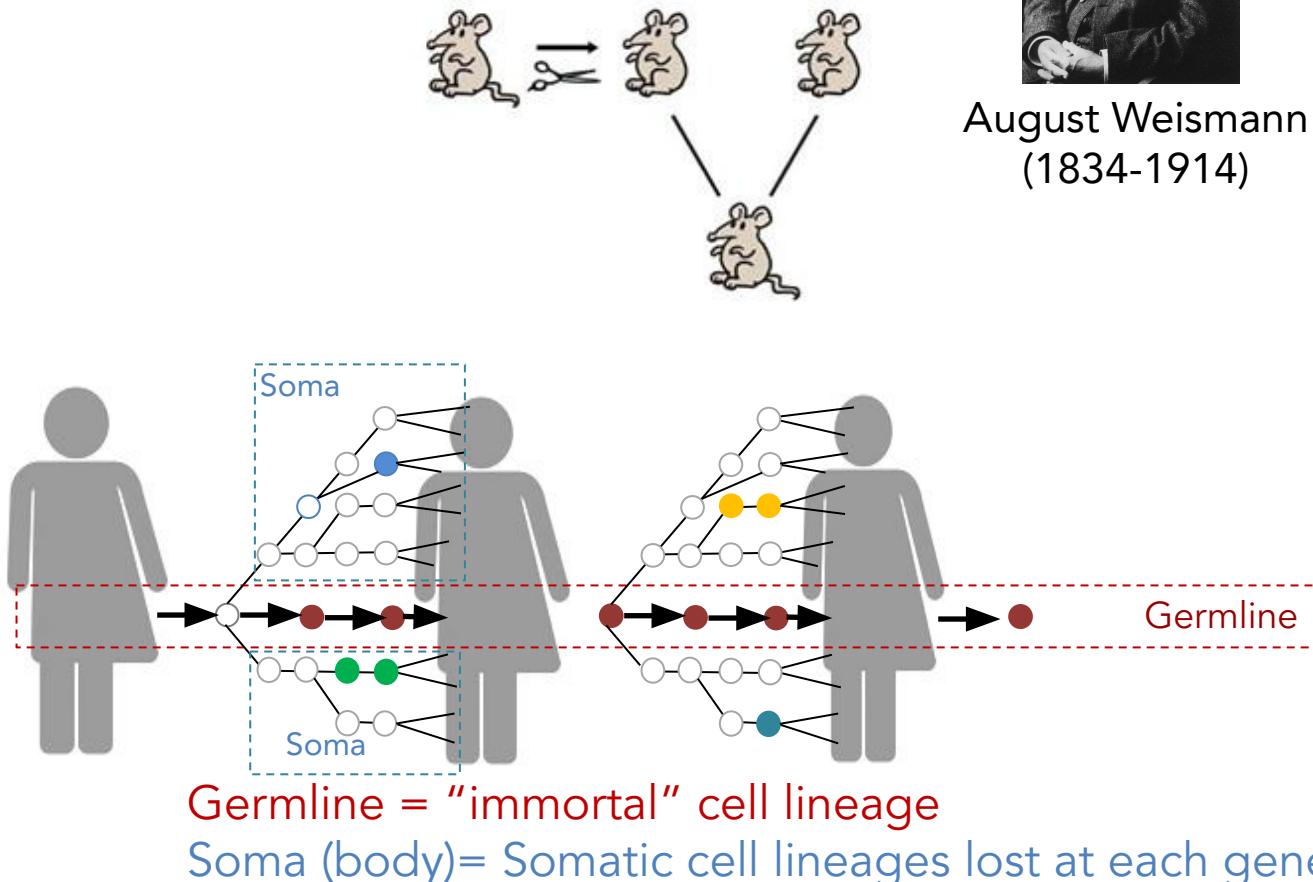
("continuity of the germ plasm" = germ cell)

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

Courtesy of Visual Image Presentations/National Library of Medicine.

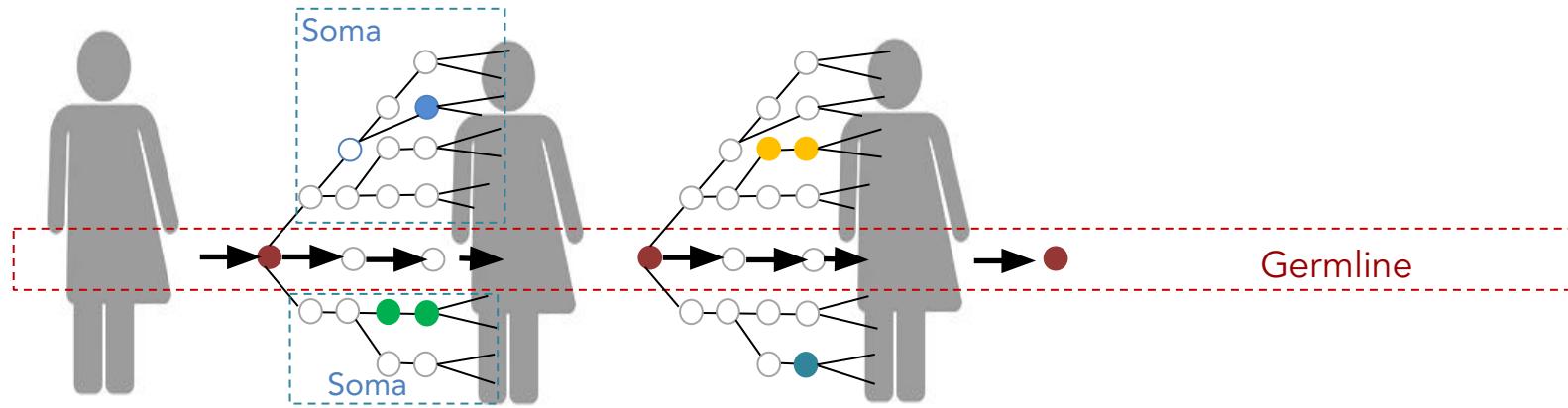
Weismann's theory: Germline vs. soma

Study of the inheritance of mutilations
(Weismann, 1888)



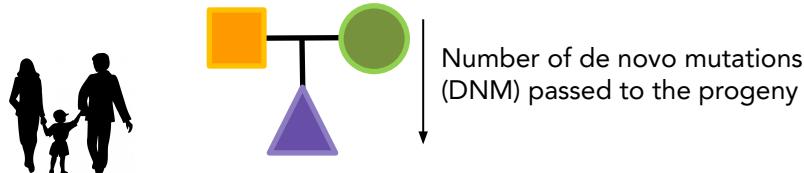
August Weismann's germ plasm theory: hereditary information moves only from germline cells to somatic cells (=somatic mutations are not inherited)

Heritable mutation rates (new mutations on the germline)



Study of heritable mutation rates: Trio sequencing

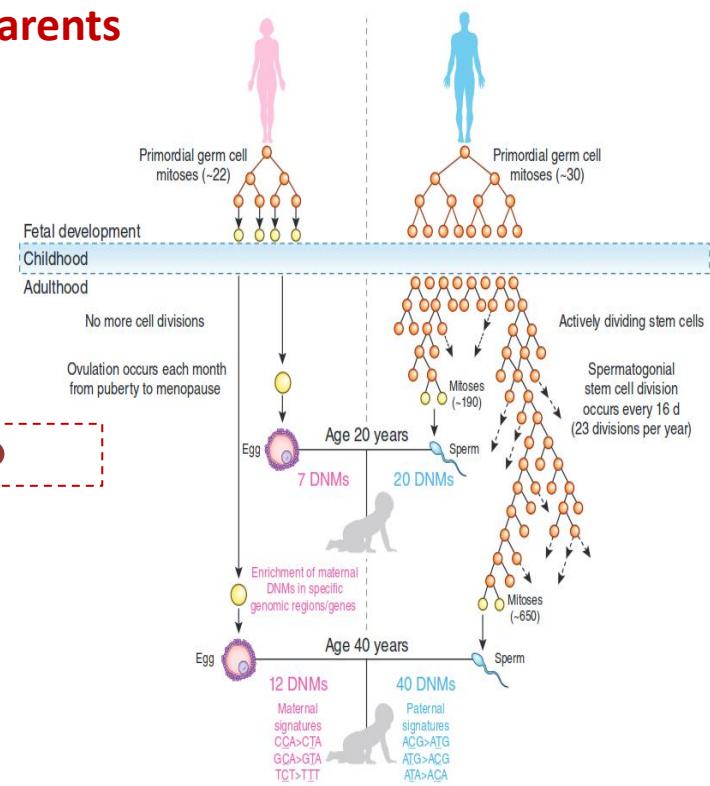
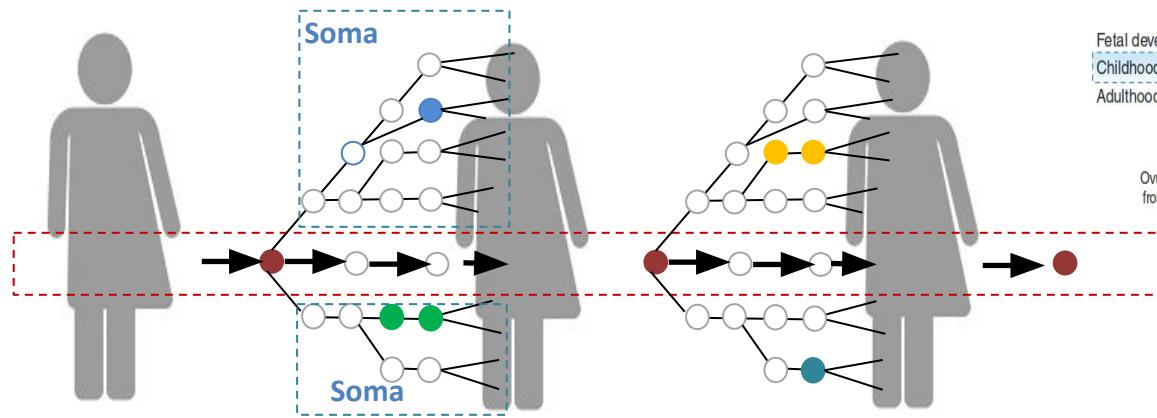
DNA sequencing of the two parents + one child (~50X) & detection of de novo mutations (DNMs)



x 1,548
Icelanders
families
Jónsson et al.
2017 Nature

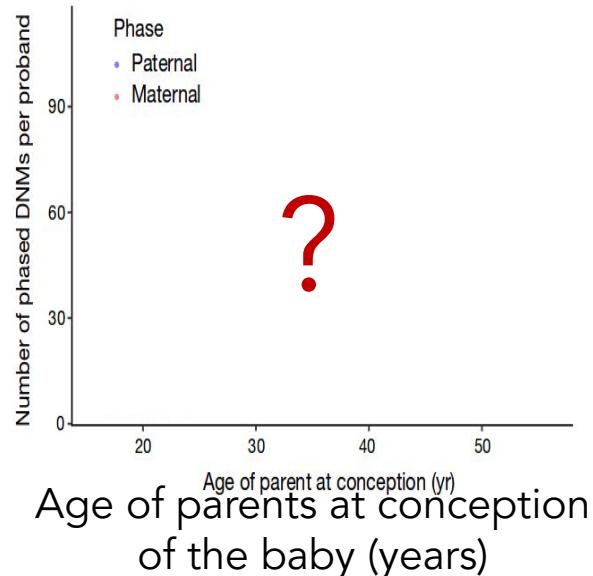
New mutations can be easily and unambiguously detected using classic bioinformatic tools (variant callers such as GATK, Samtools, ...)

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



Study of heritable mutation rates: Trio sequencing

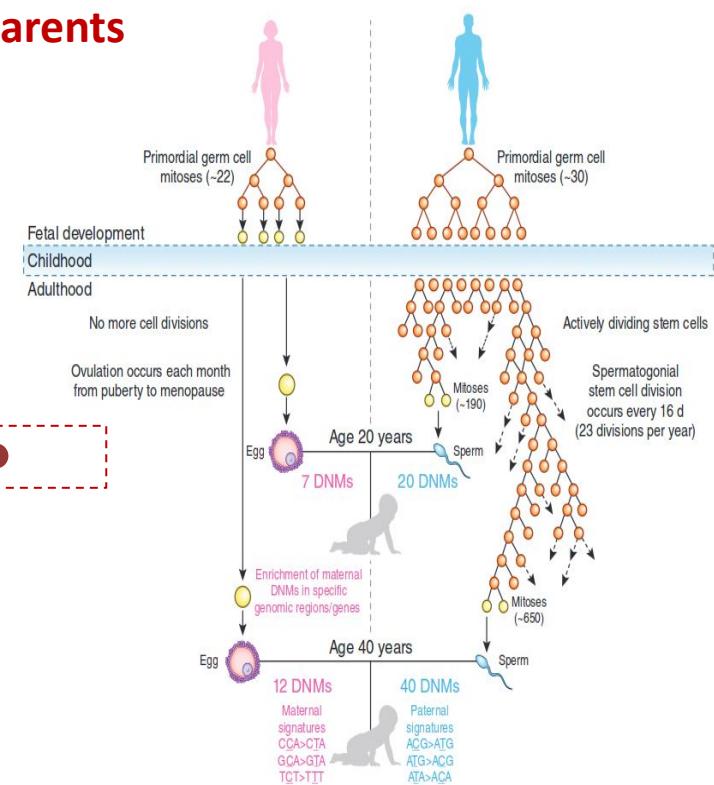
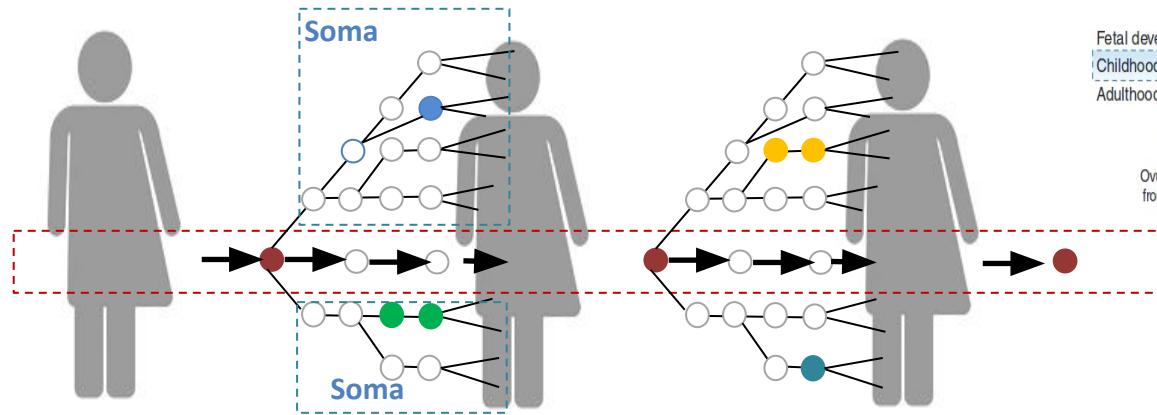
Number of *de novo* mutations identified in the child



Goldmann et al. 2016 Nature Genetics
Goriely 2016 Nature Genetics

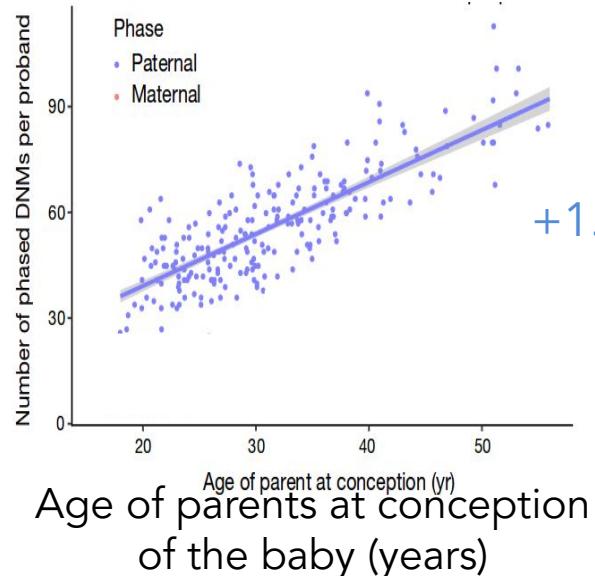
Jónsson et al. 2017 Nature (see also Kong et al. 2012 Nature)

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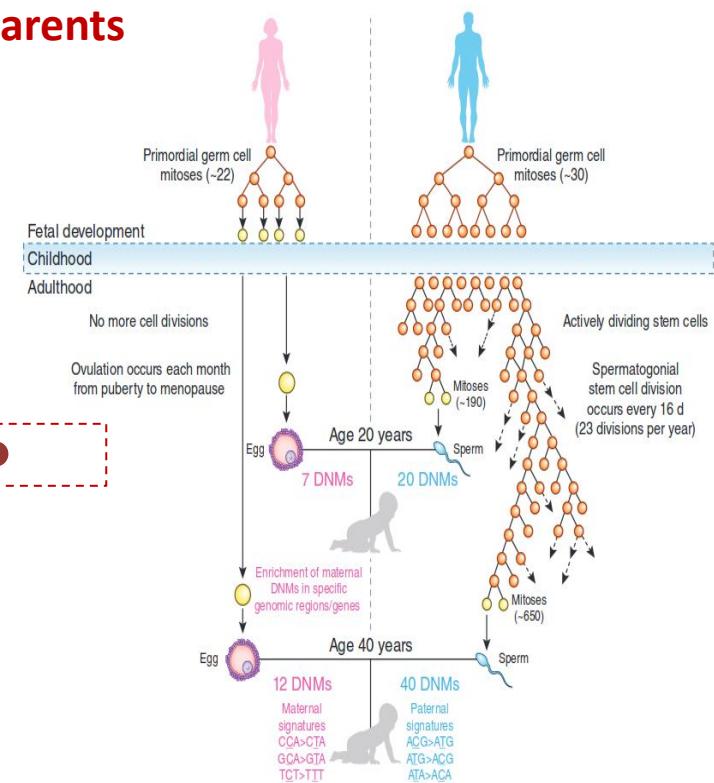
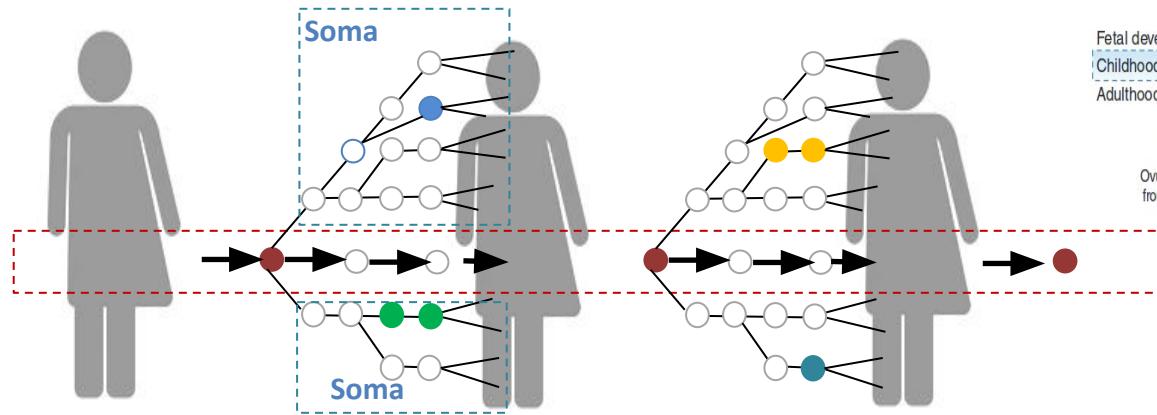
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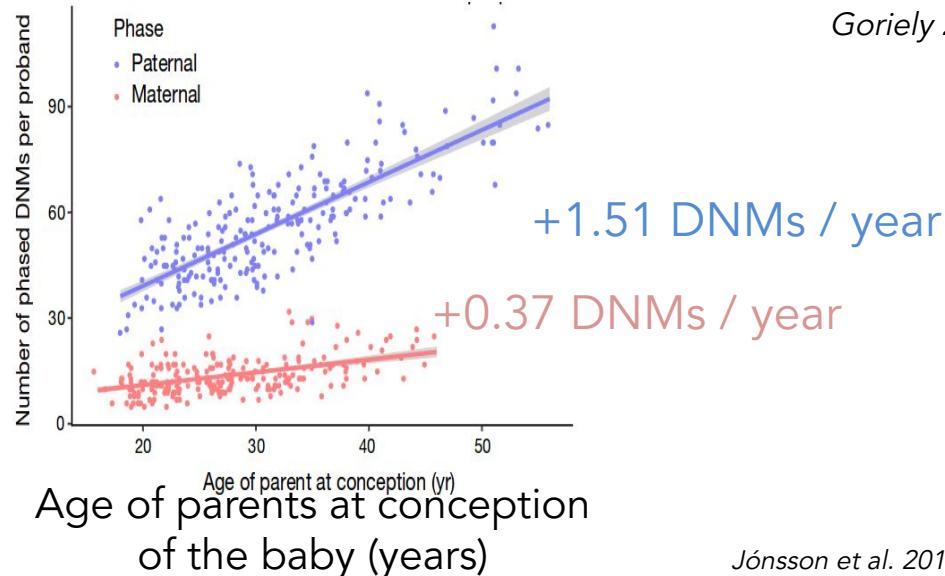
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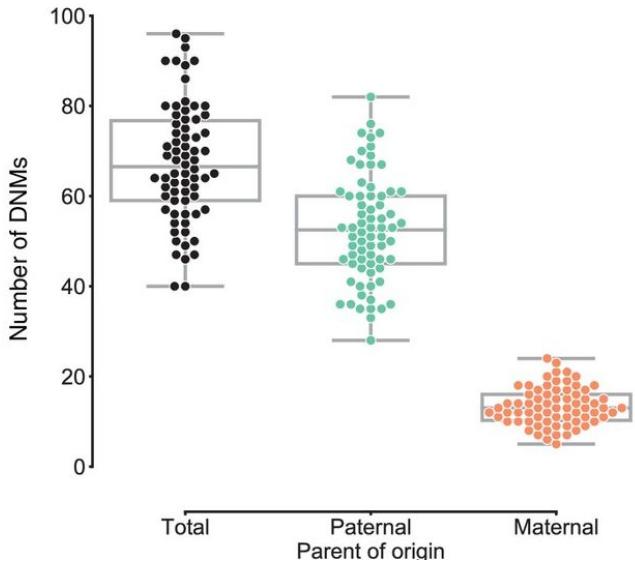
Goldmann et al. 2016 Nature Genetics
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Summary: animal germline mutations (heritable mutations)

Sex-specific pattern:

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

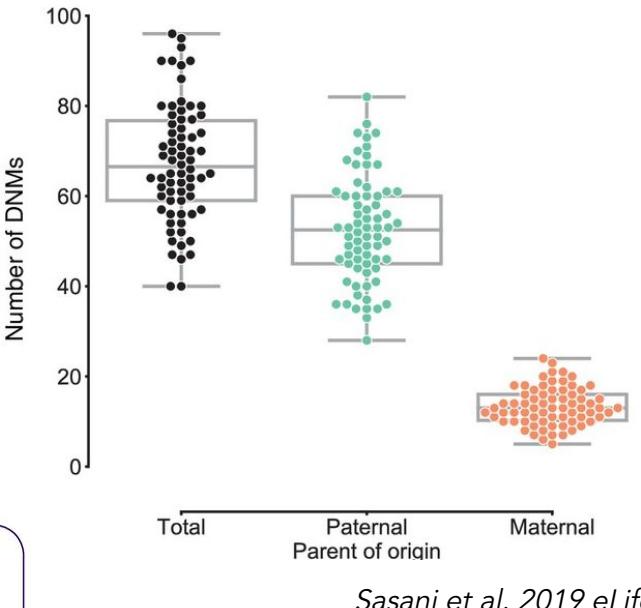


Sasani et al. 2019 eLife

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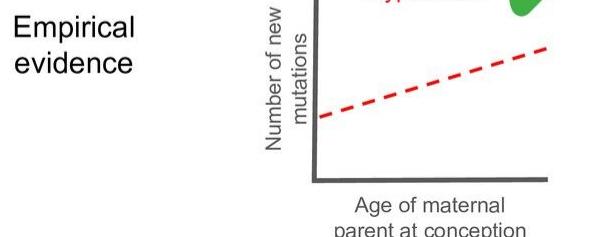
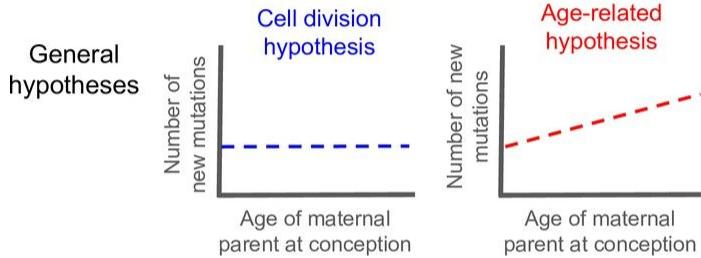
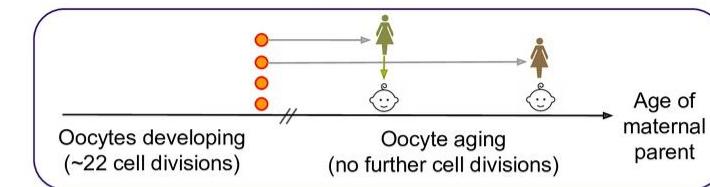


Sasani et al. 2019 eLife

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!



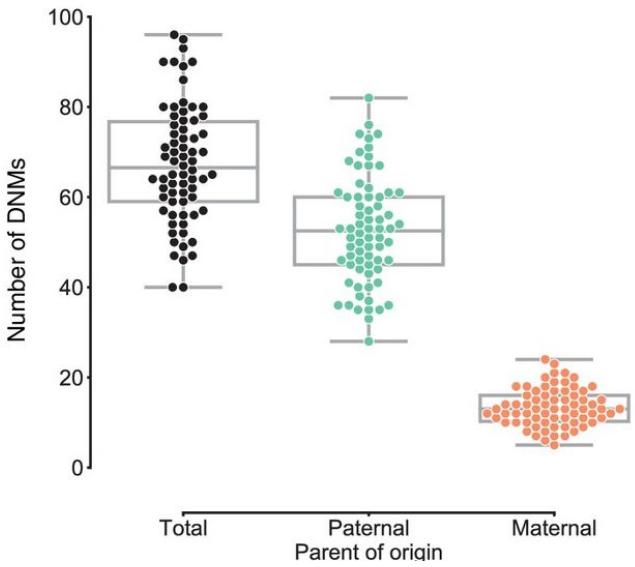
Unrepaired damage accumulating with age

Leroy 2023, eLife

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Sasani et al. 2019 eLife

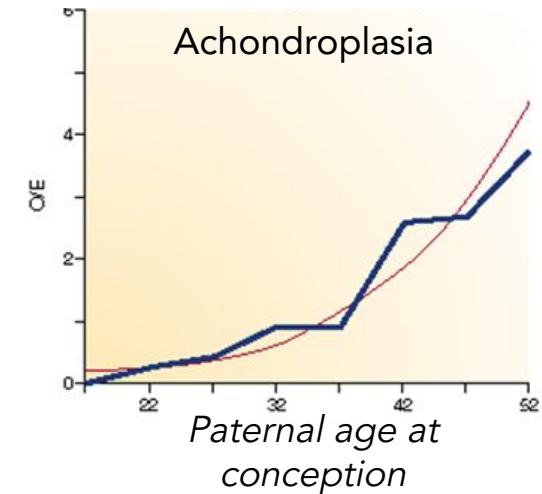
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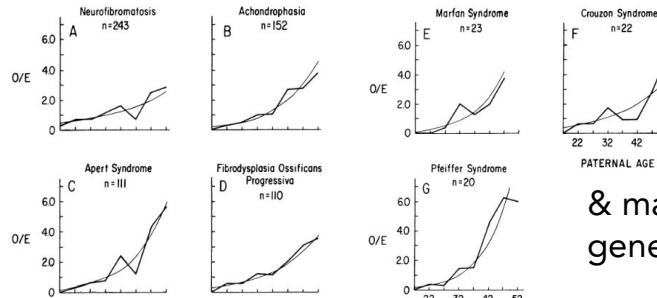
Medical consequences in humans: Sex*Age-specific pattern

"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



Crow, 2000 Nature Review Genetics



& many other genetic disorders...

Risch et al. 1987 American journal of human genetics

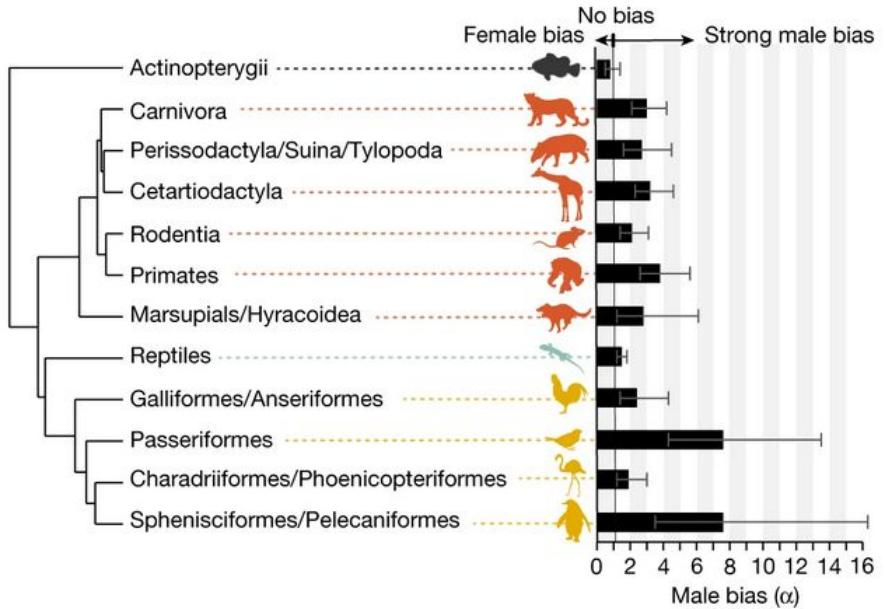
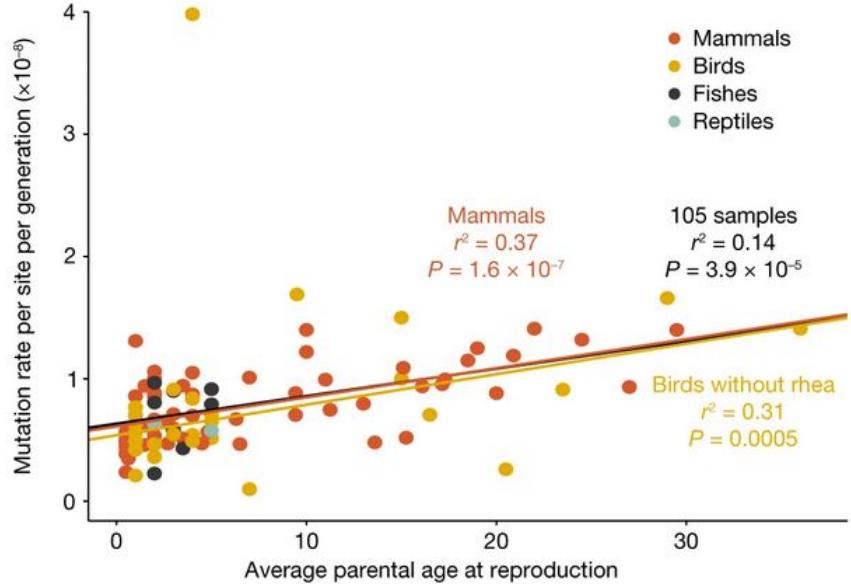
Summary: animal germline mutations



A calm couple of
Chrysemys picta

Sex- & age-specific pattern

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



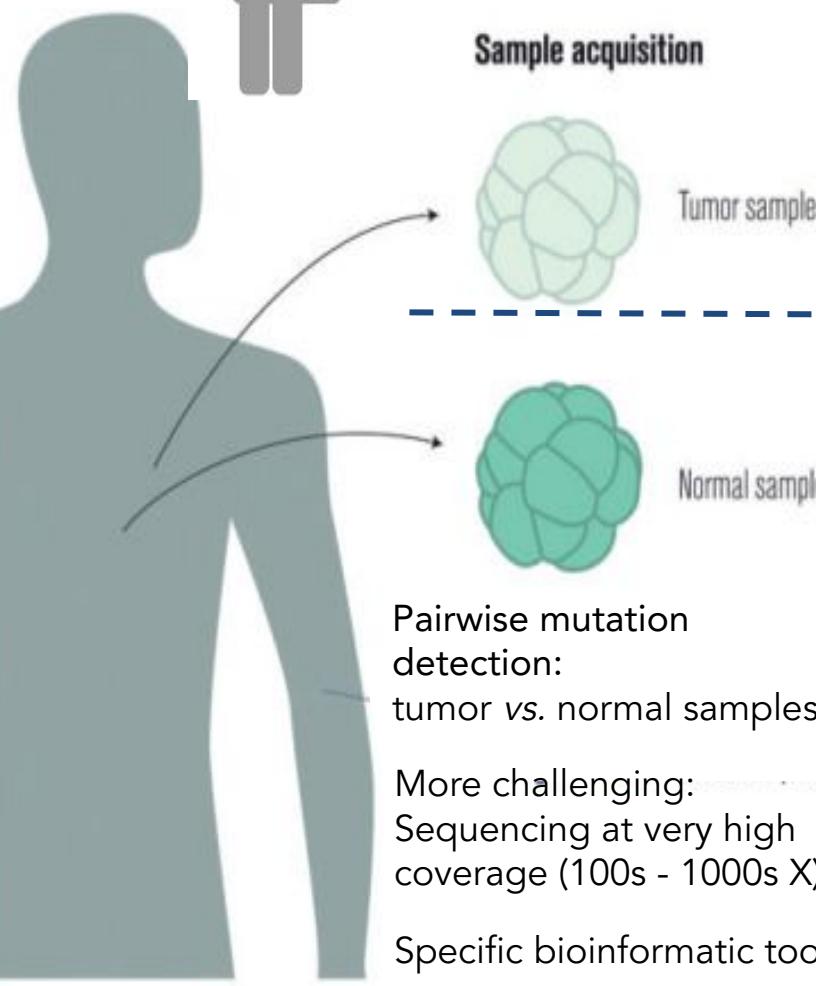
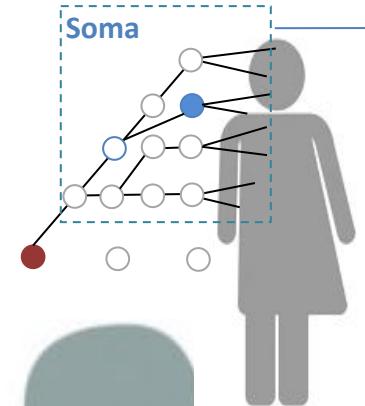
Bergeron et al. 2023 Nature

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

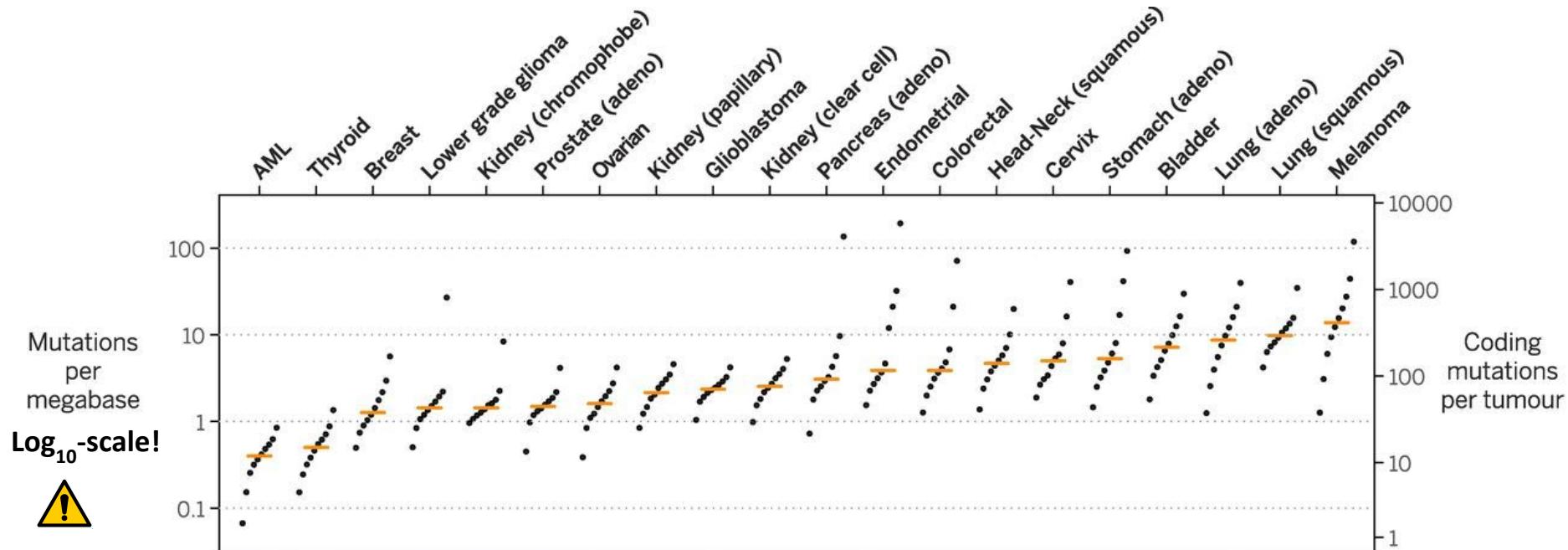


A	G	T	G	A
A	G	T	G	A
A	G	T	G	A
A	G	T	G	A
A	C	T	G	A
A	G	T	G	A
A	C	T	G	A
A	G	T	G	A
A	C	T	A	T

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

Somatic mutations and cancers

Frequency of occurrence of new mutations

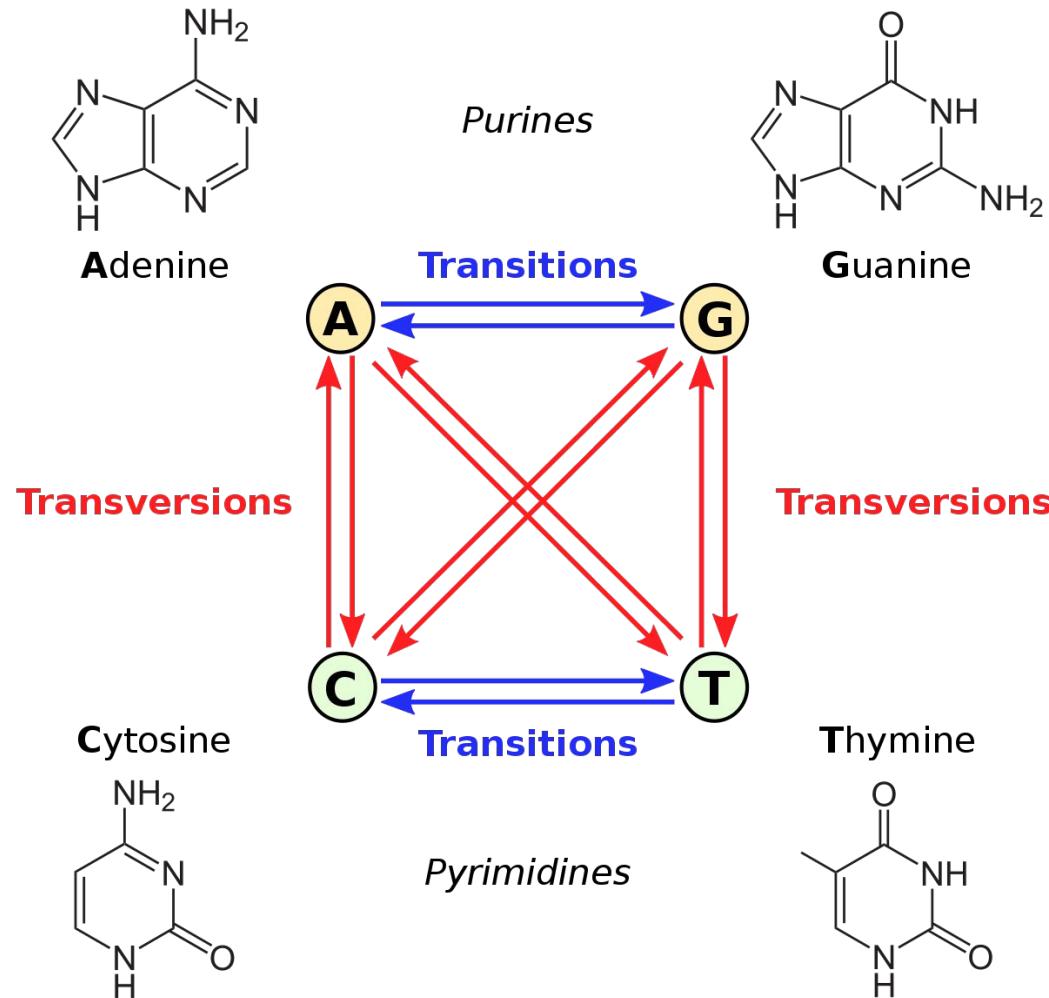


Mutation rates are highly variable depending on the tumor samples, because mutations do not occur at the same pace depending on the tissues

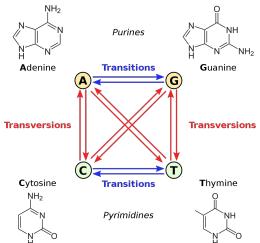
-> Importance of mutagens, i.e. UV for melanoma!

Somatic mutations and cancers

Mutational signatures (mutation spectra)

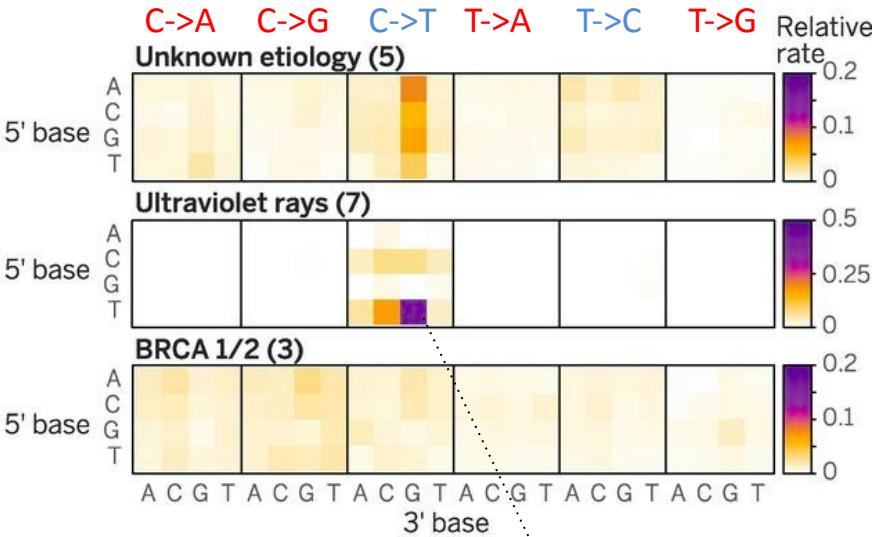
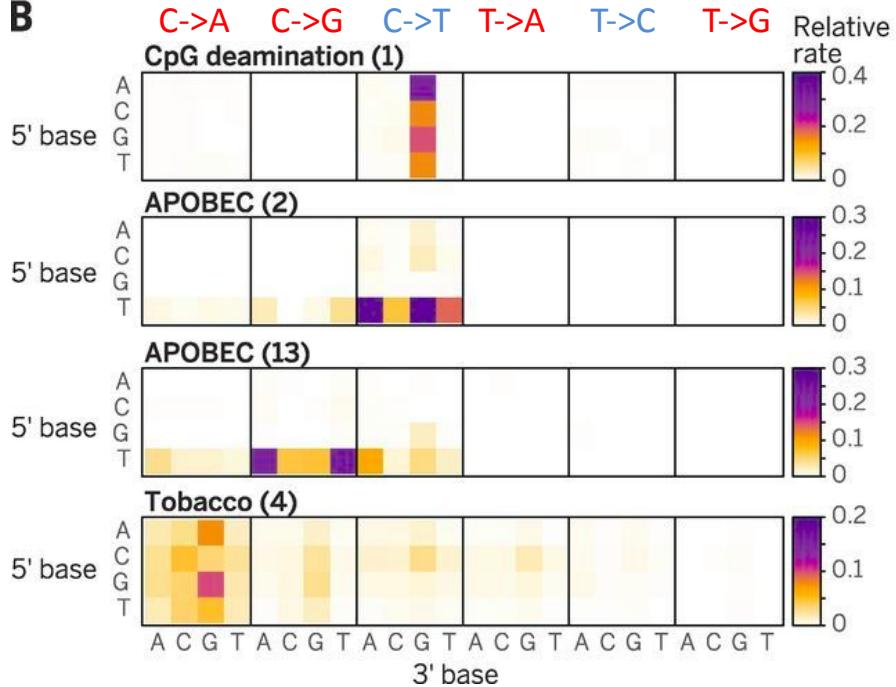


Somatic mutations and cancers



Mutational signatures (mutation spectra)

B



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

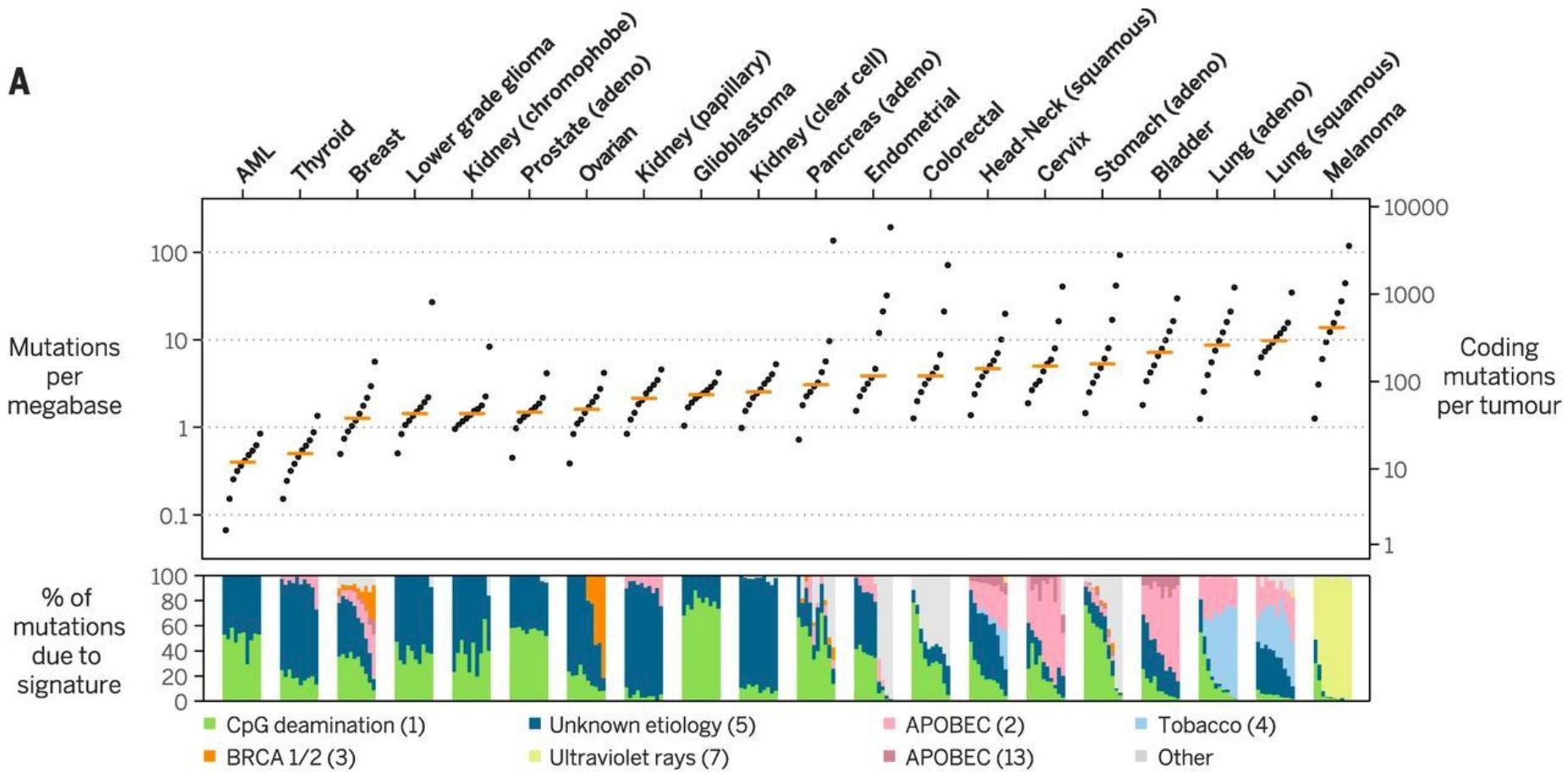
Mutation is a random process but highly dependent on the genomic context

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

Somatic mutations and cancers

Frequency of occurrence and mutational signatures

A

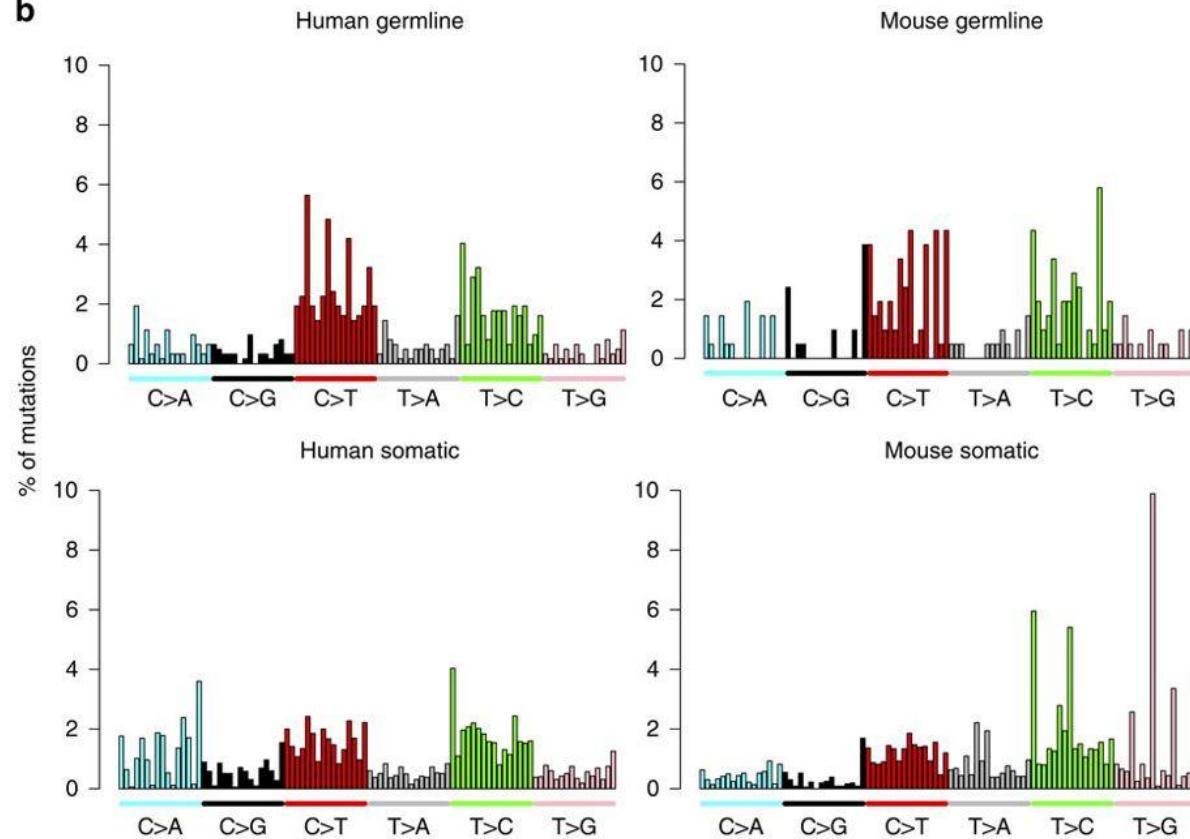


Summary: somatic and germline mutations

b

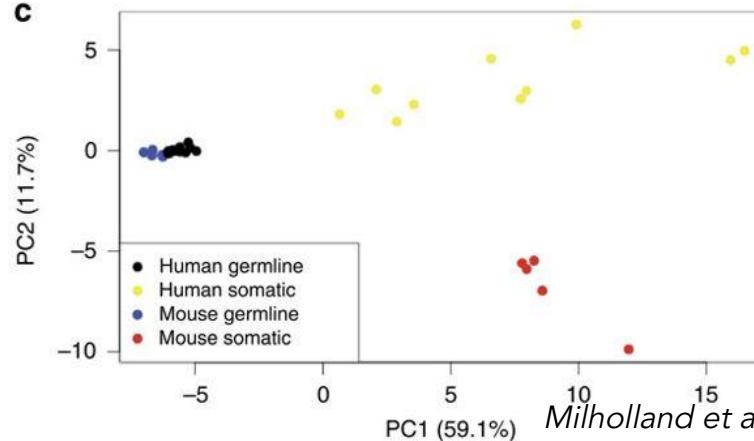
Mutation is a random process, but...

... 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.

c



Summary: somatic and germline mutations

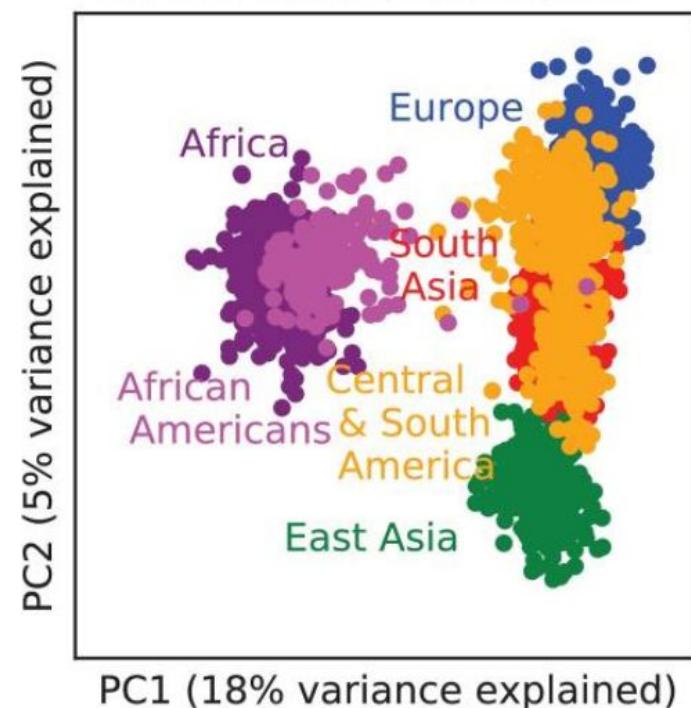
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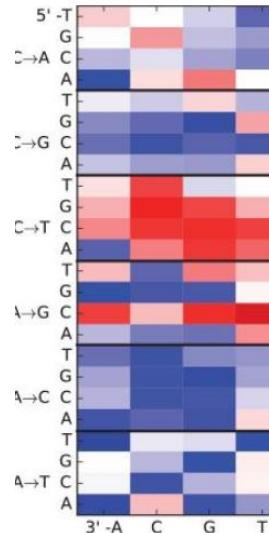
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Even at relatively short evolutionary time, it seems! Here an example for the evolution of the germline mutation spectra in humans

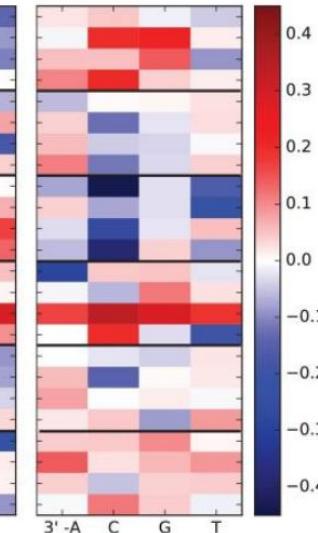
A. PCA of human mutation spectra



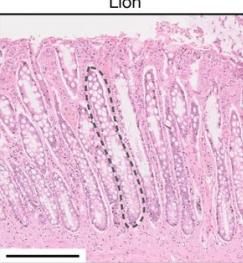
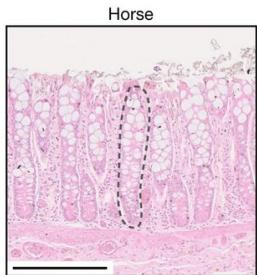
B. PC1 Loading



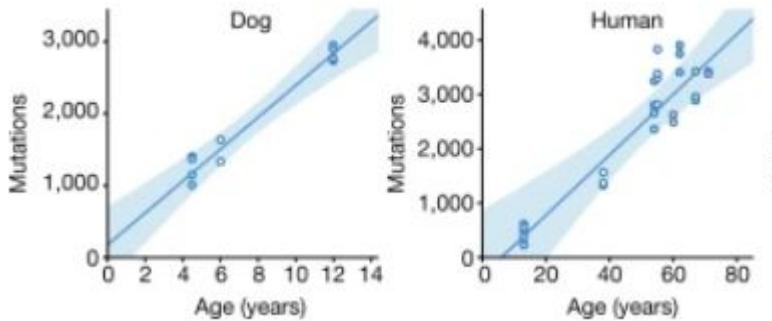
C. PC2 Loading



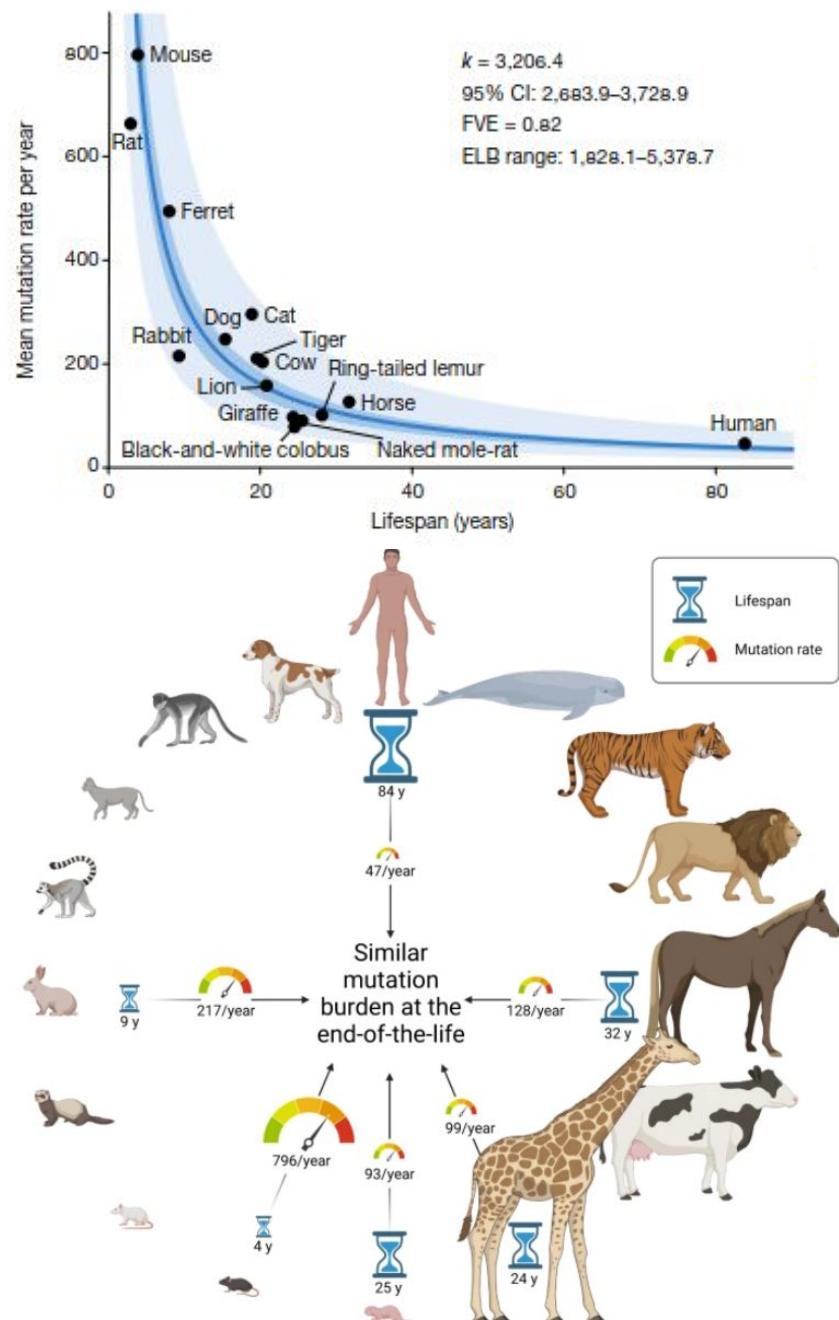
Perspective: somatic rates and life span



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



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)

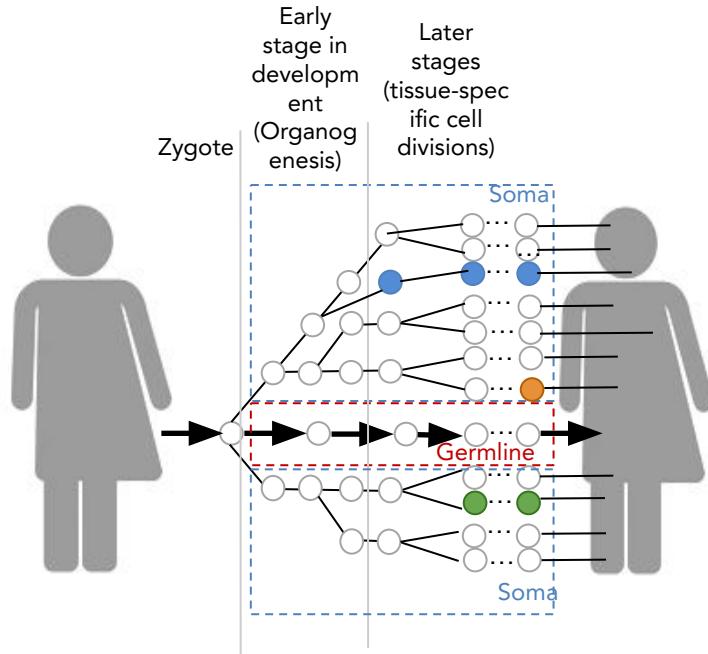
Heritable mutations in animals =
germline mutations = meiotic mutations +
mitotic mutations on germinal cells

?

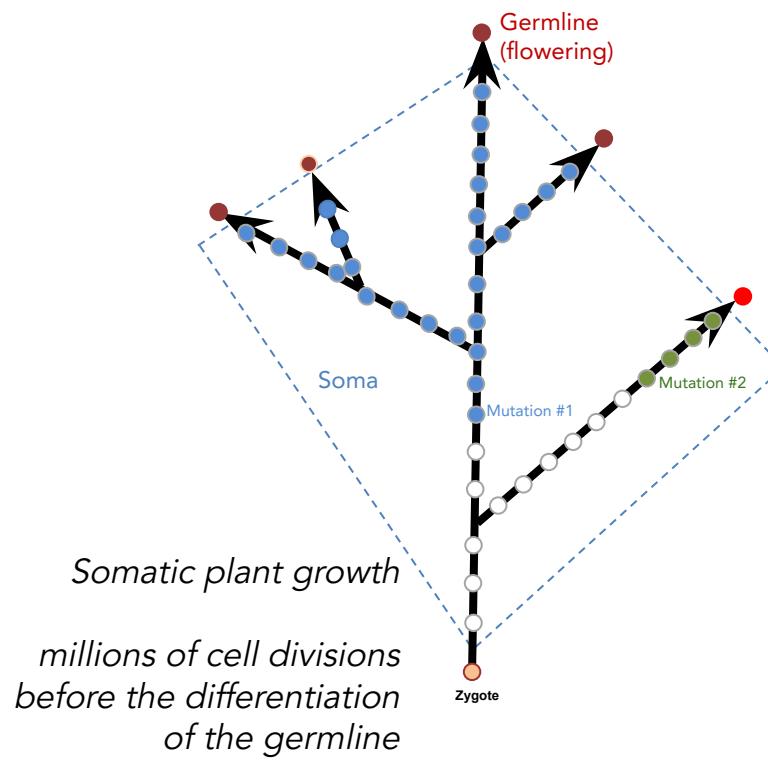
Other somatic mutations are not heritable

General expectation: plants depart from the Weismann's theory

Animal model



Plant model



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

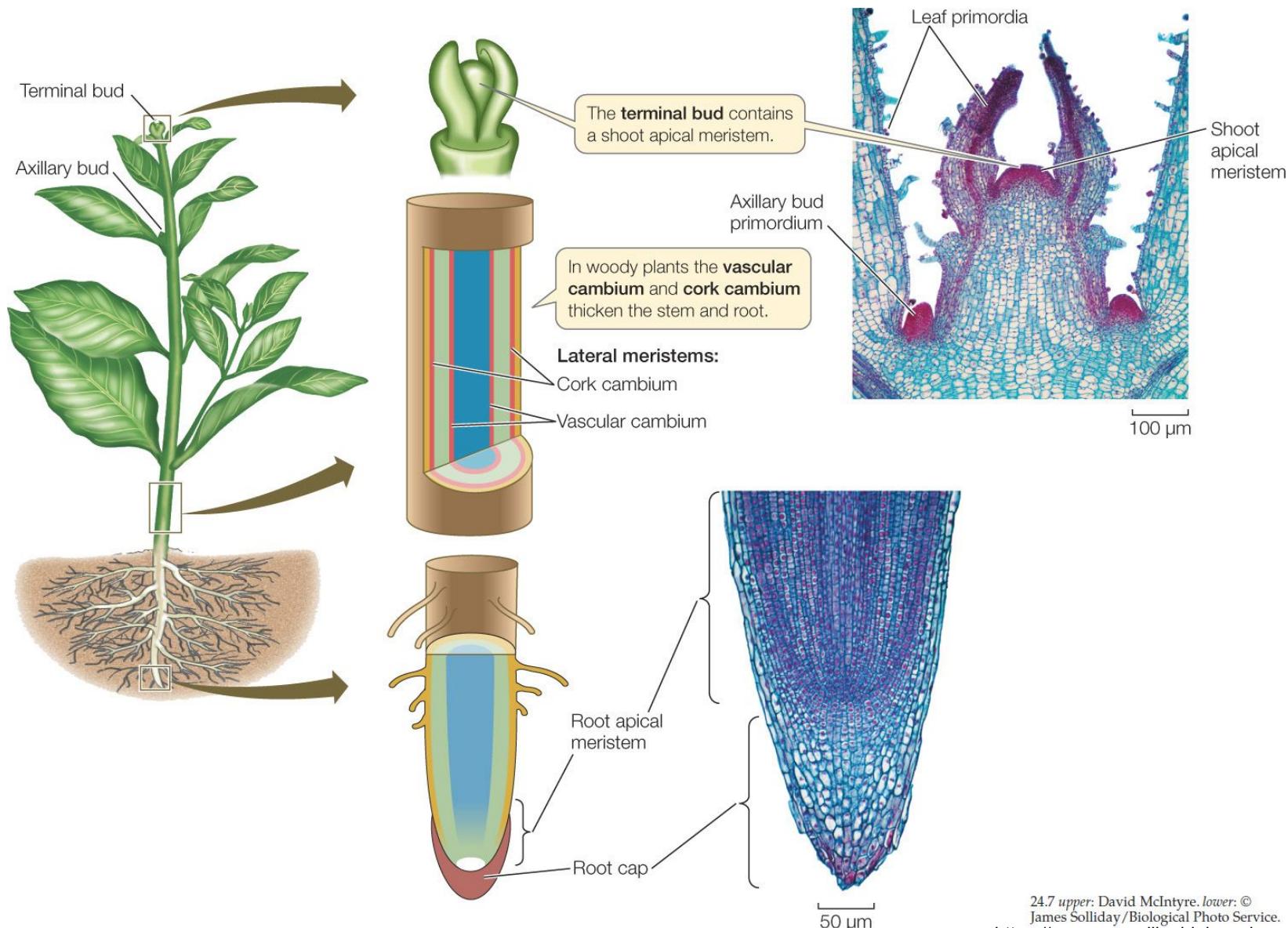


This is a general hypothesis

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

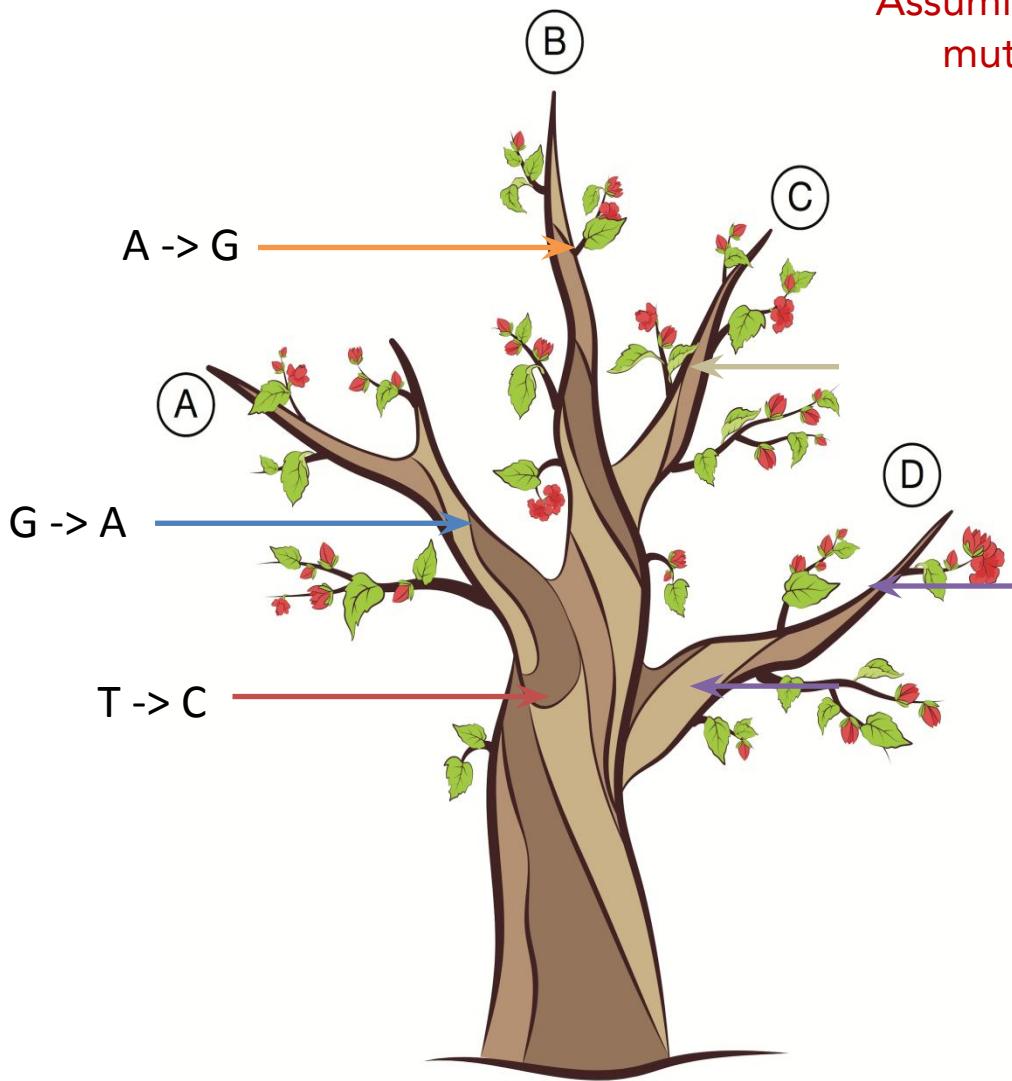
General expectations for plants

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

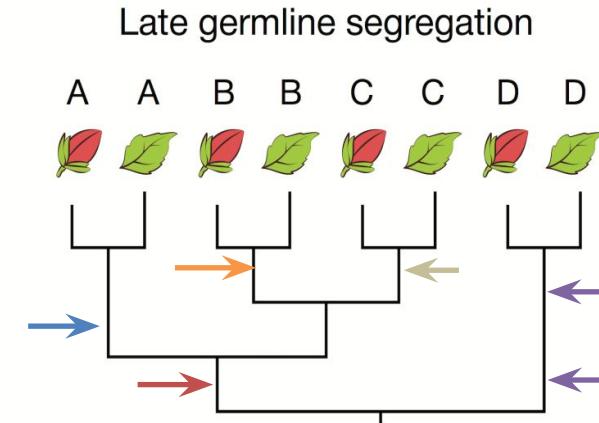


24.7 upper: David McIntyre, lower: © James Soliday/Biological Photo Service.
<https://www.macmillanhighered.com> (24.2)

General expectations for plants



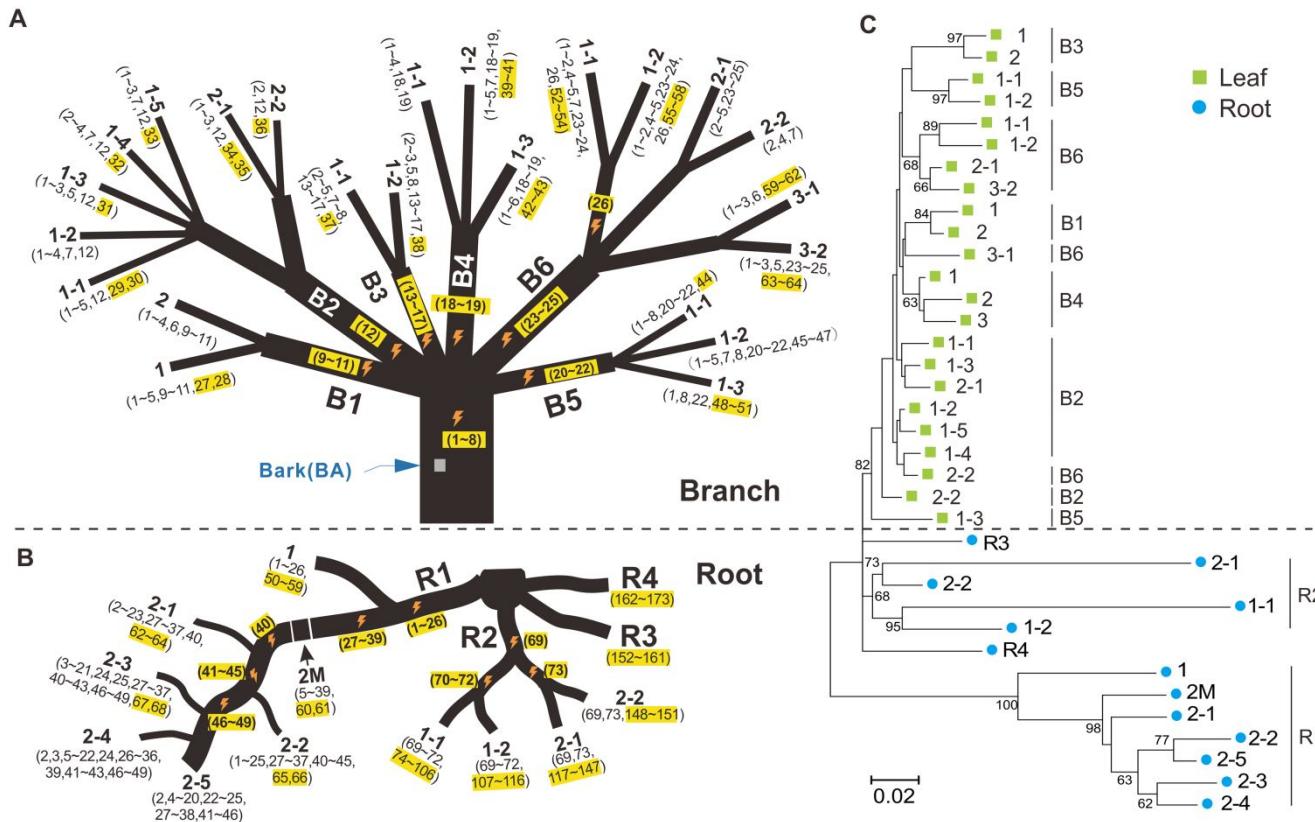
Assuming a late germline segregation for plants,
mutations accumulate along growth axes!



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

A typical example in *Prunus*

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

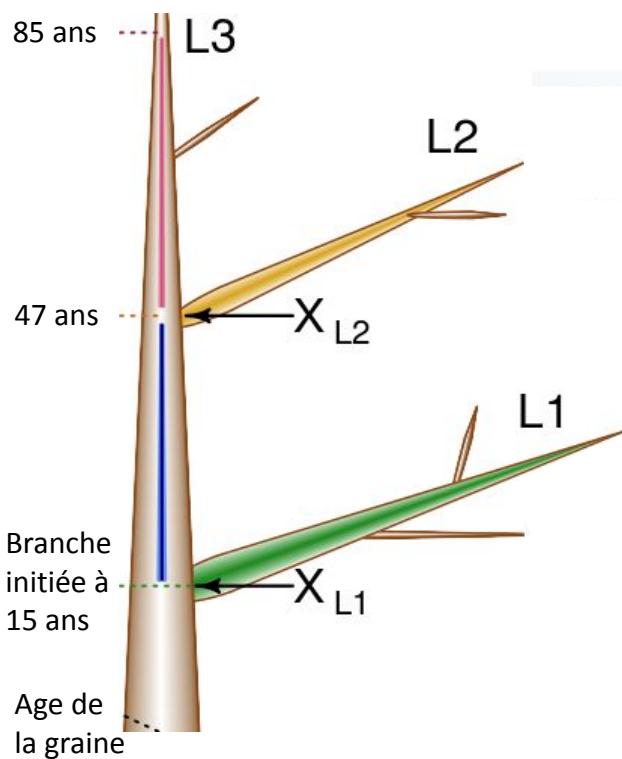


Lower mutation rates in shoots: a way to keep heritable mutation rates under control?

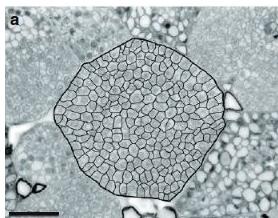
Far more mutations detected in roots than in shoots!

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

First empirical evidences: "3P" oak tree in Pierrotin



3 samples sequenced at 160X



When a new somatic mutation occurs:
 $\text{freq (alt)} = 1 / 2N$
meristematic cells

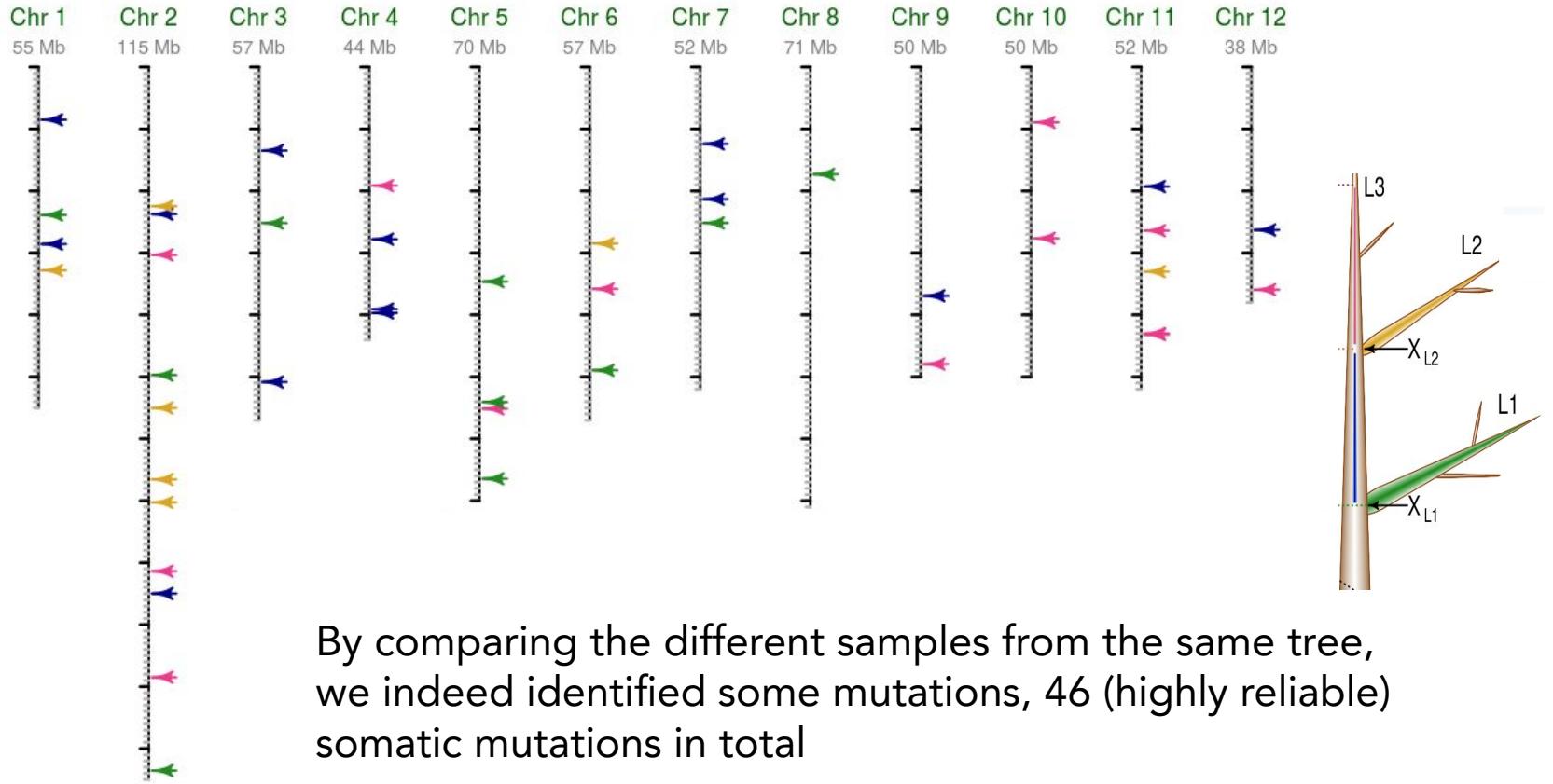
Schmid-Siegert et al.
2017, Nature plants

(assuming 20 meristematic cells, freq ~ 0.025)



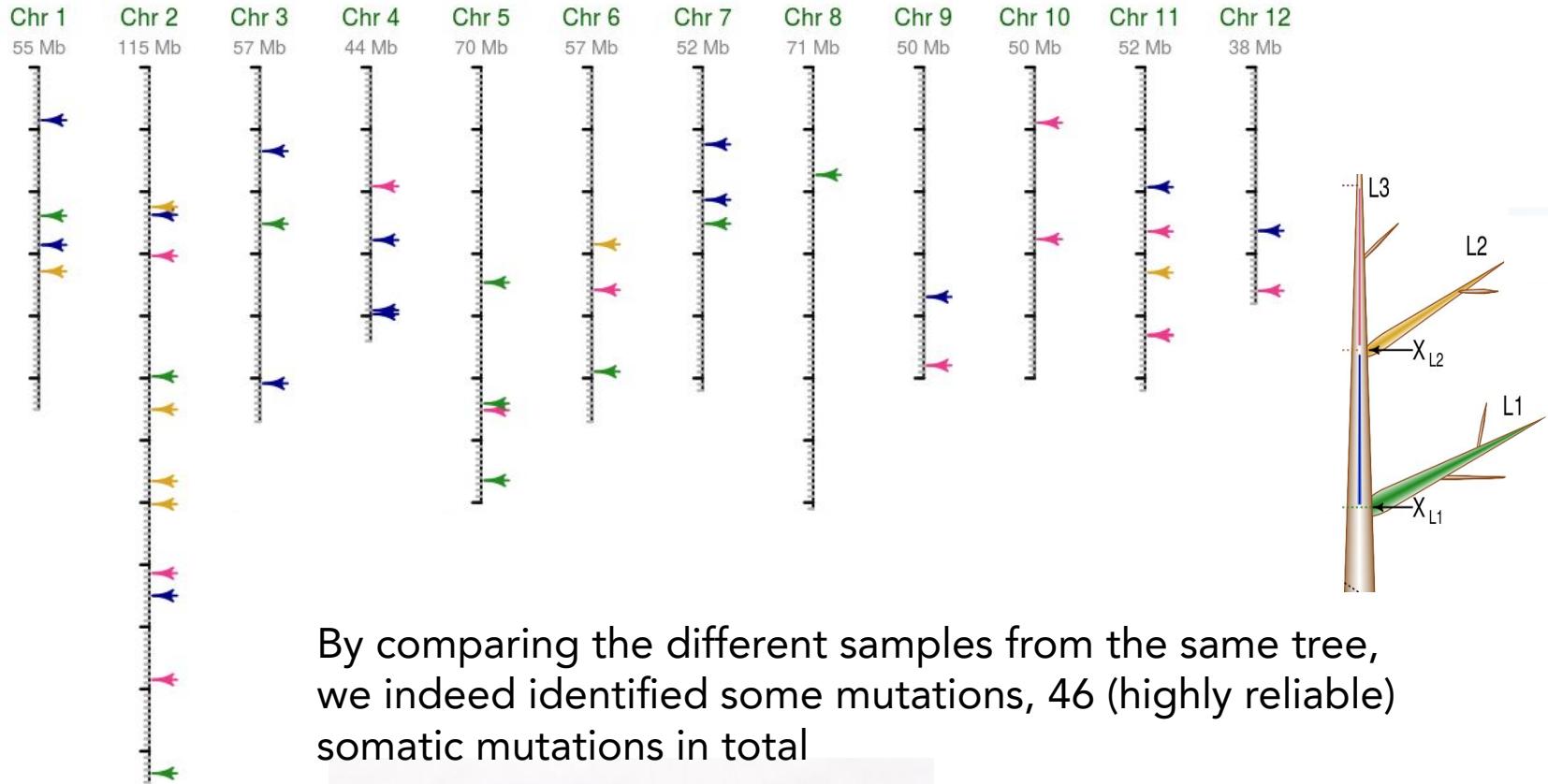
Require variant calling using software adapted for low-frequency mutations
(similar to somatic mutation in cancer)

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



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

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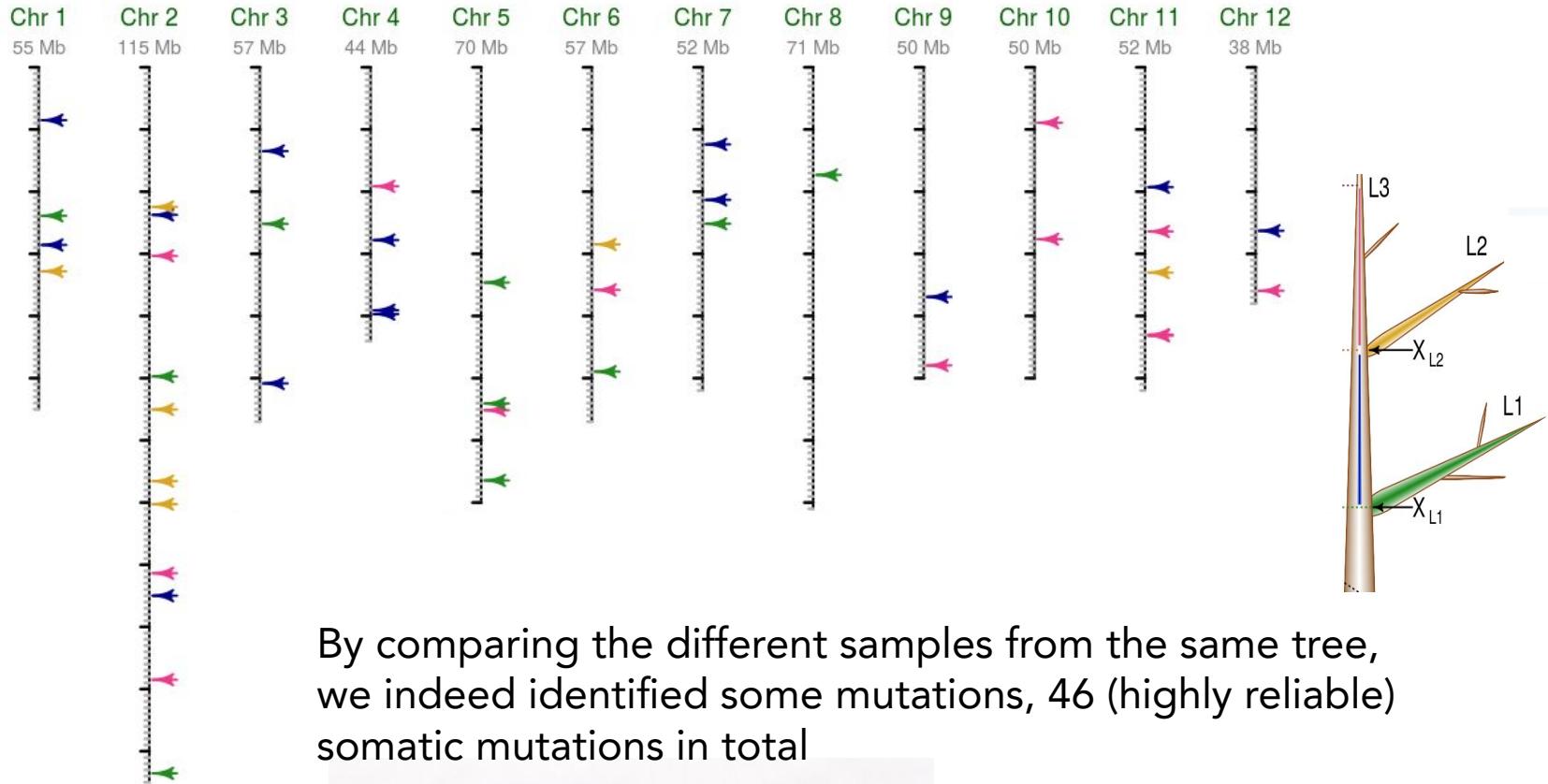
Extremely rare events

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



Study of the mutation process

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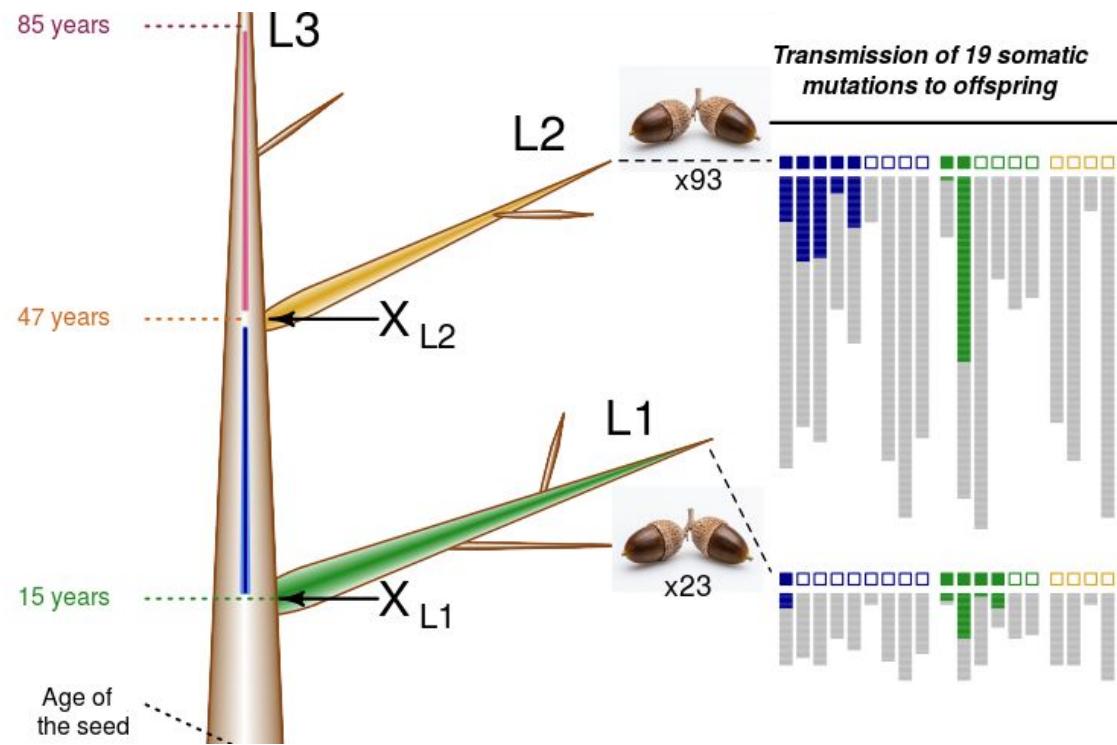
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Study of the mutation process



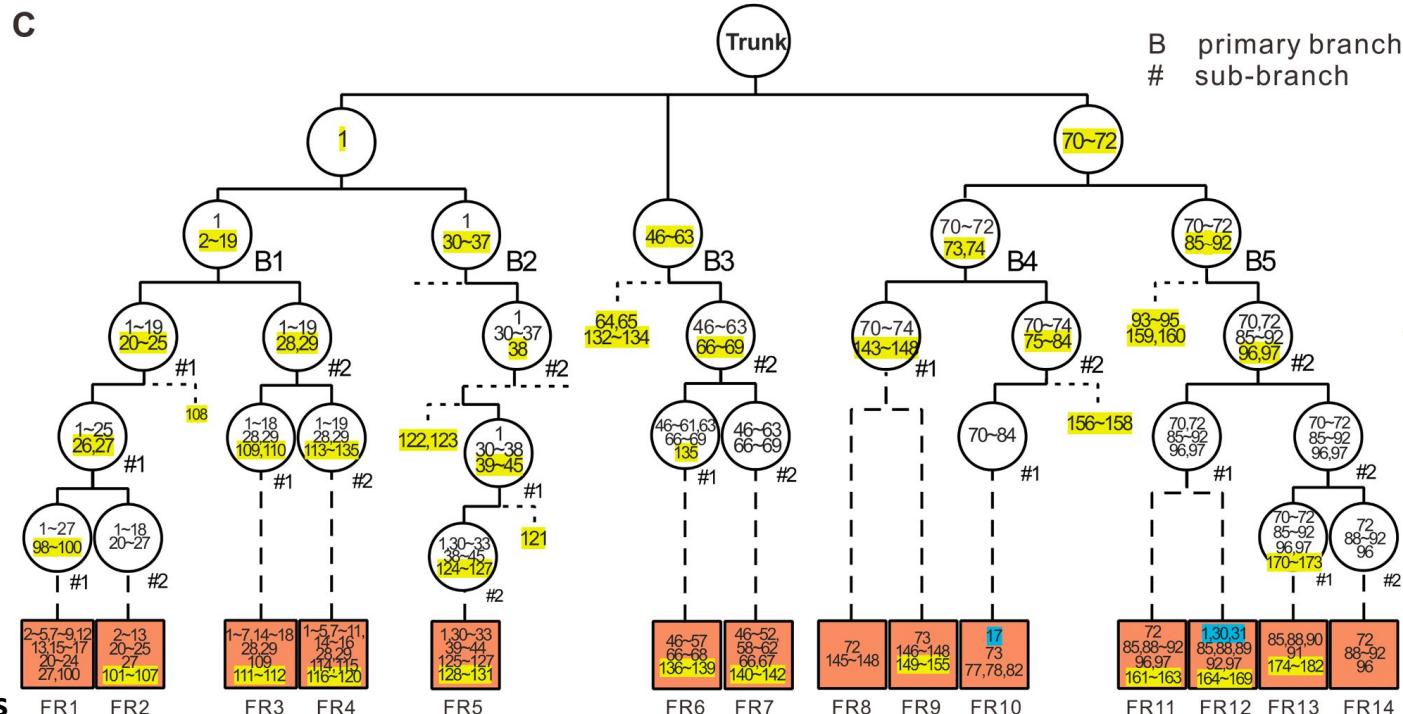
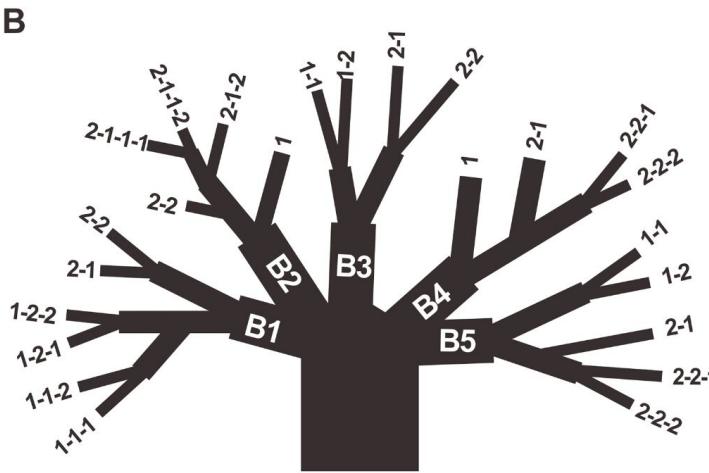
Are somatic mutations passed to the progeny?



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

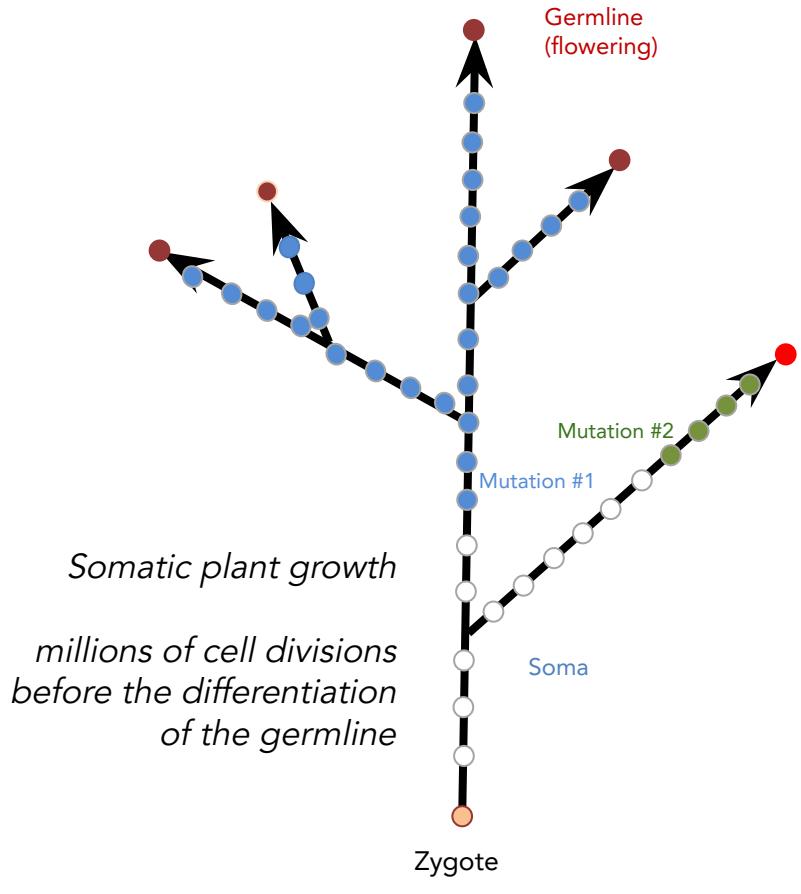
In agreement with the general hypothesis for plants

Are somatic mutations passed to the progeny?



modified from Wang et al. 2019 PLoS Biology

Summary: plant mutations (up to now)



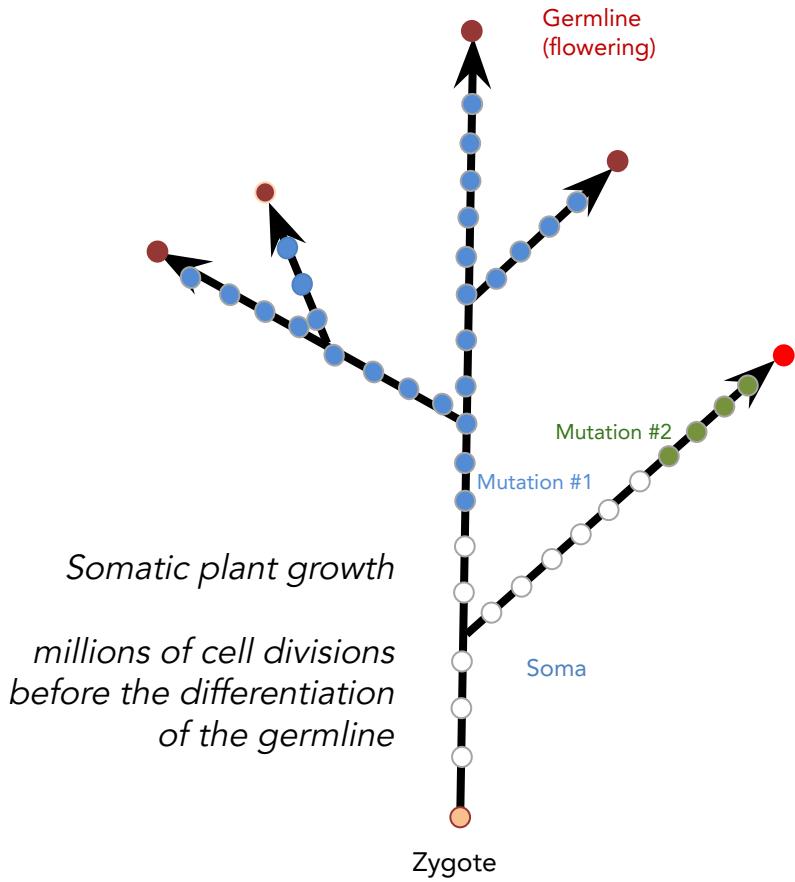
A mutation happens in a population of cells (a meristem): a methodological challenge
It requires to adapt methods initially developed for cancer genomics

Mutation accumulate along plant growth

Somatic mutation can be passed to the progeny in plants

Summary: plant mutations (up to now)

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



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

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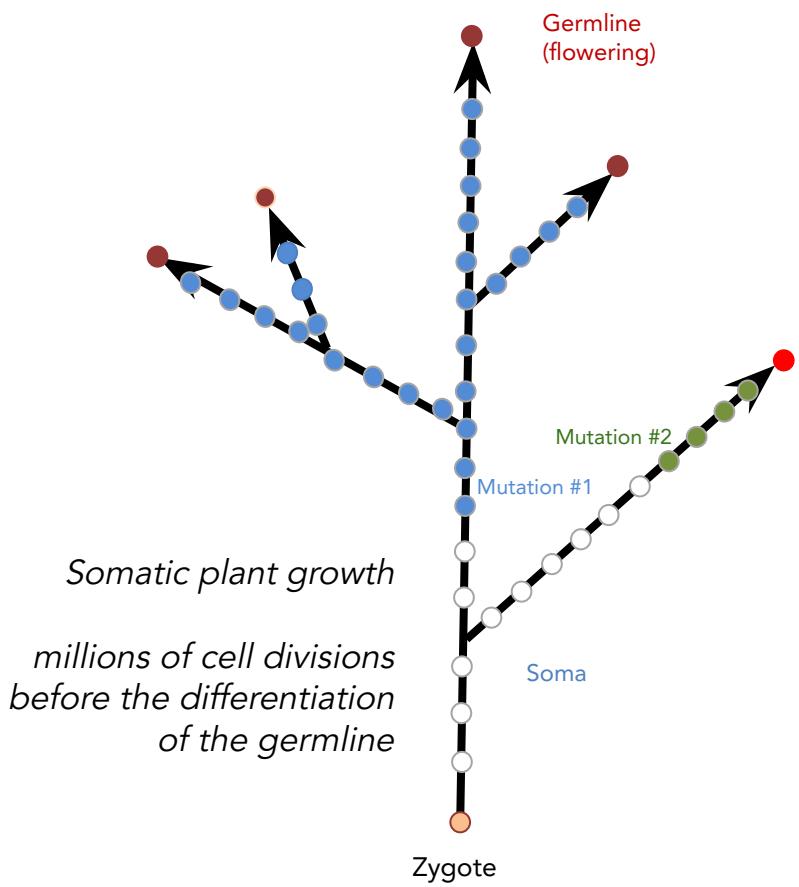
→ Does this vary depending on the tissues?
Are mutations generated by DNA replication or DNA repair errors?

Somatic mutation can be passed to the progeny in plants

→ Does this apply to all plants?

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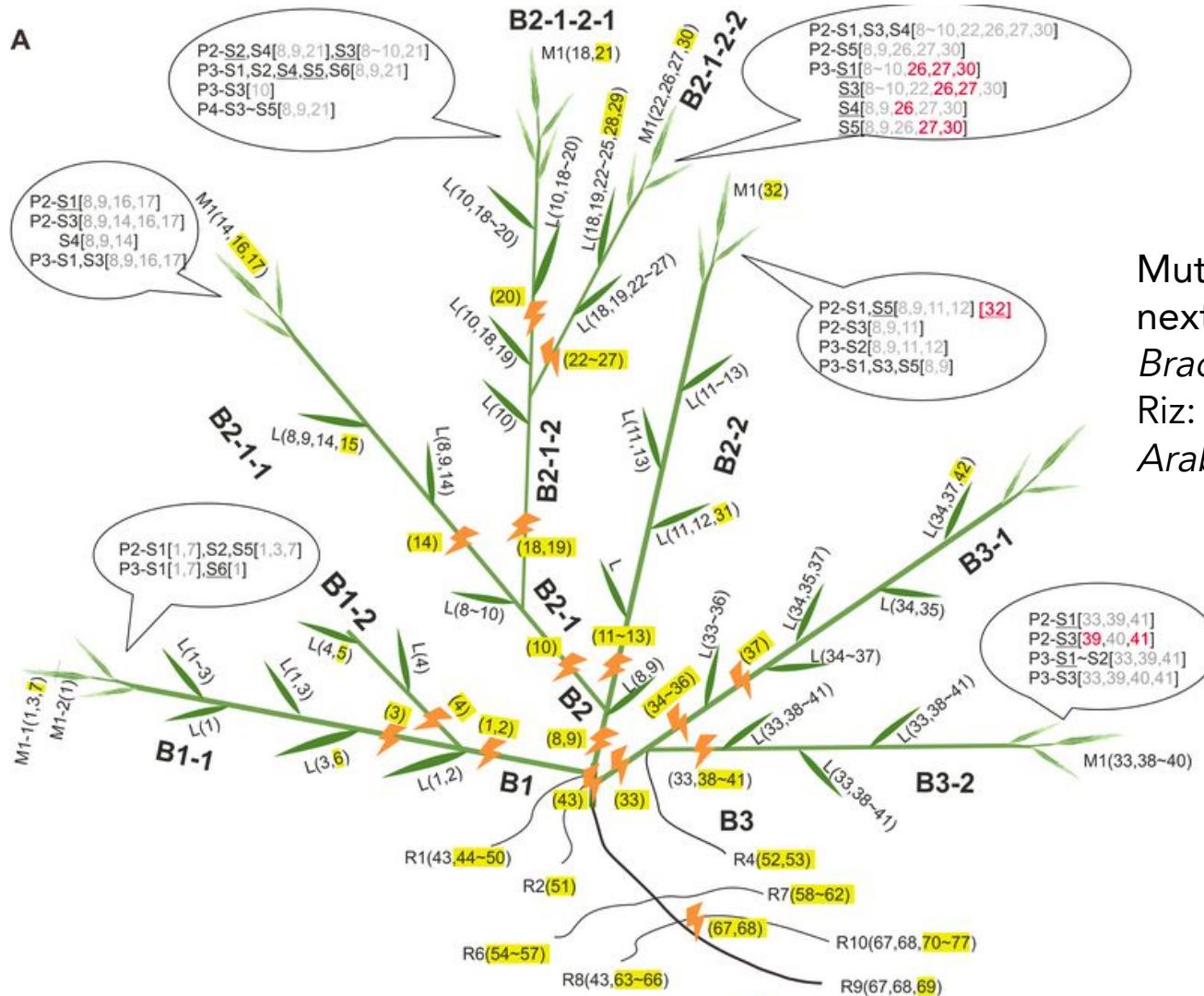
Mutation accumulate along plant growth

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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?

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

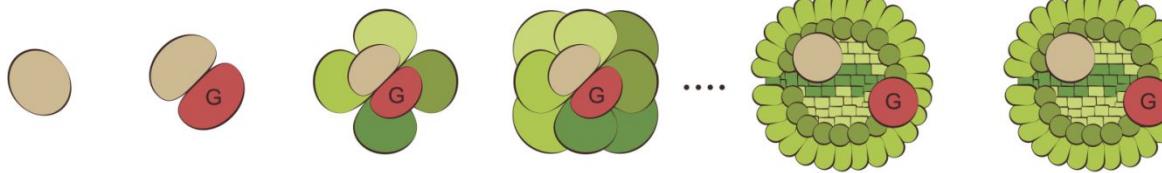
(A) Late segregation, late differentiation



(B) Early segregation, late differentiation



(C) Early segregation, early differentiation

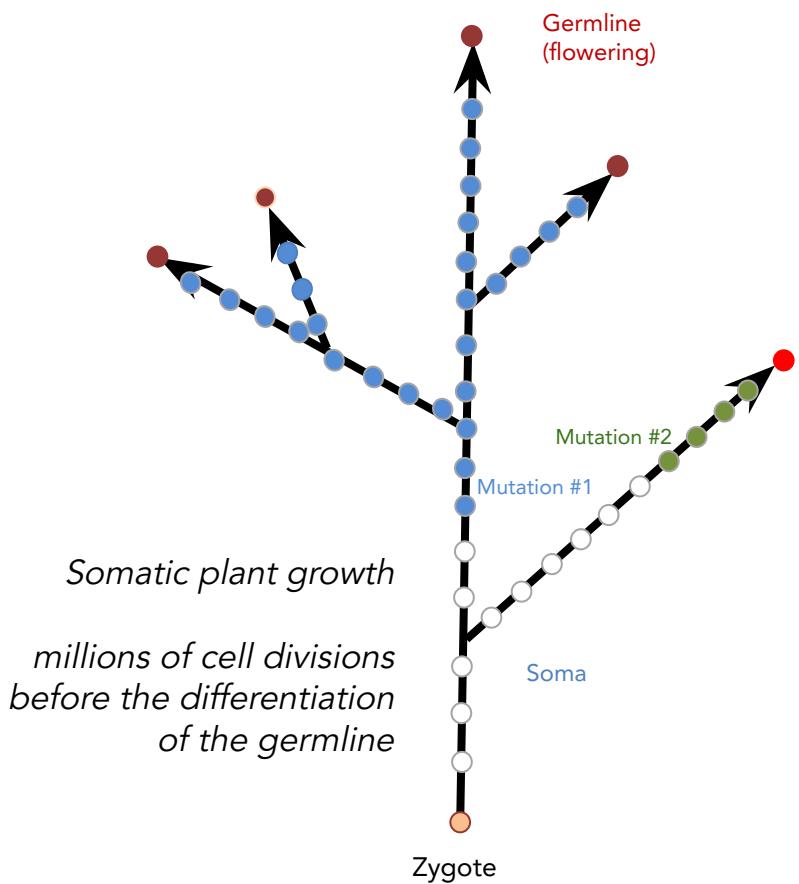


- G Segregated germline cell lineage
- Undifferentiated stem cell
- Differentiated somatic cell
- Differentiated germline cell

"[...] 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"

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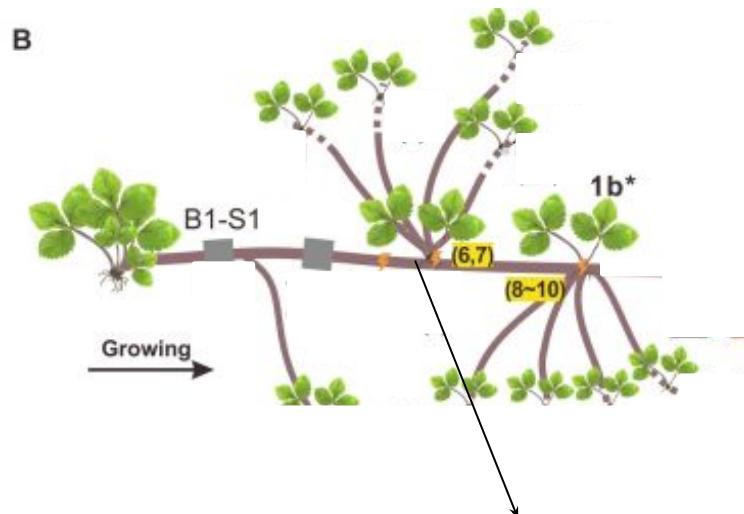
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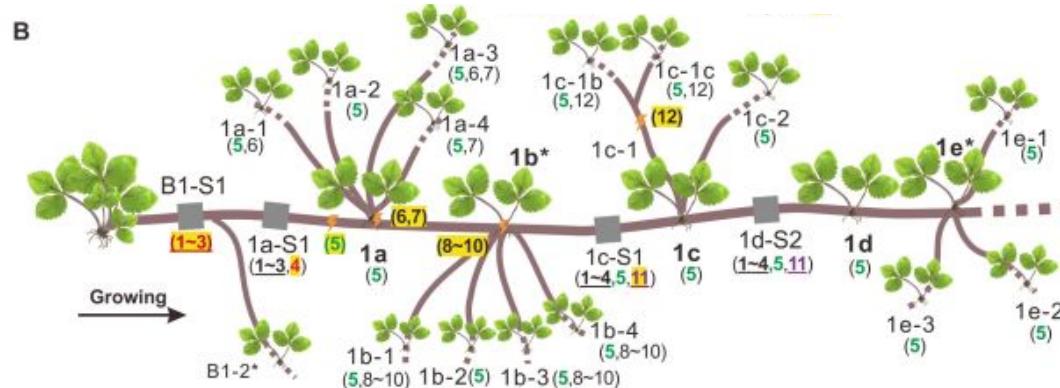
Somatic mutation can be passed to the progeny in plants

→ Does this apply to all plants?

Mutations accumulated along growth? Which growth?



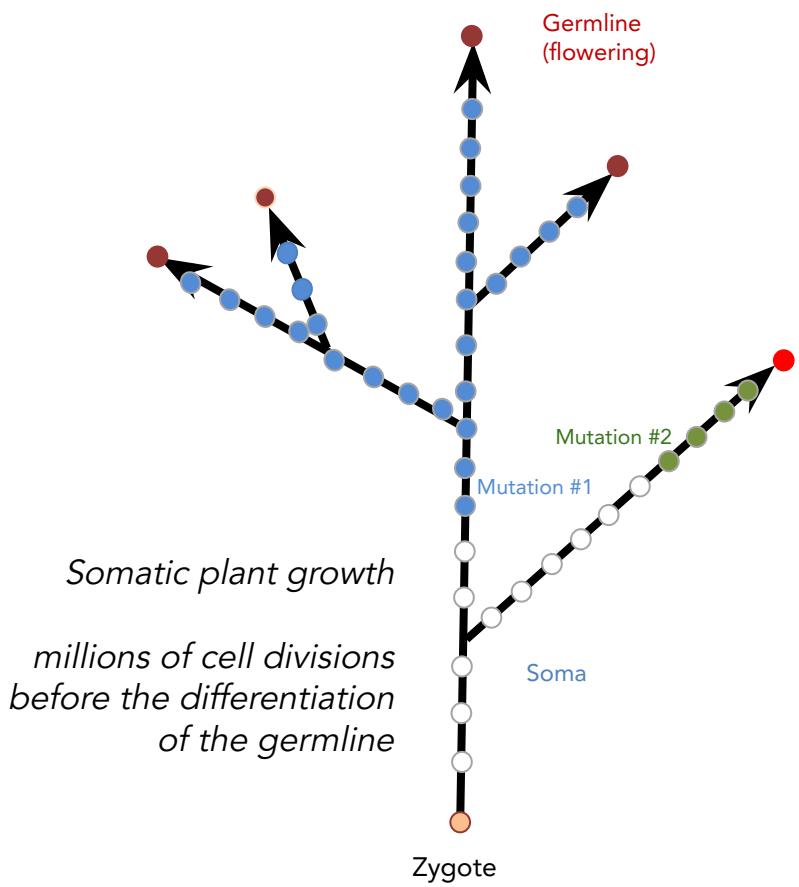
Runners (« stolons »)
= Vegetative propagation



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

Summary: plant mutations (up to now)

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



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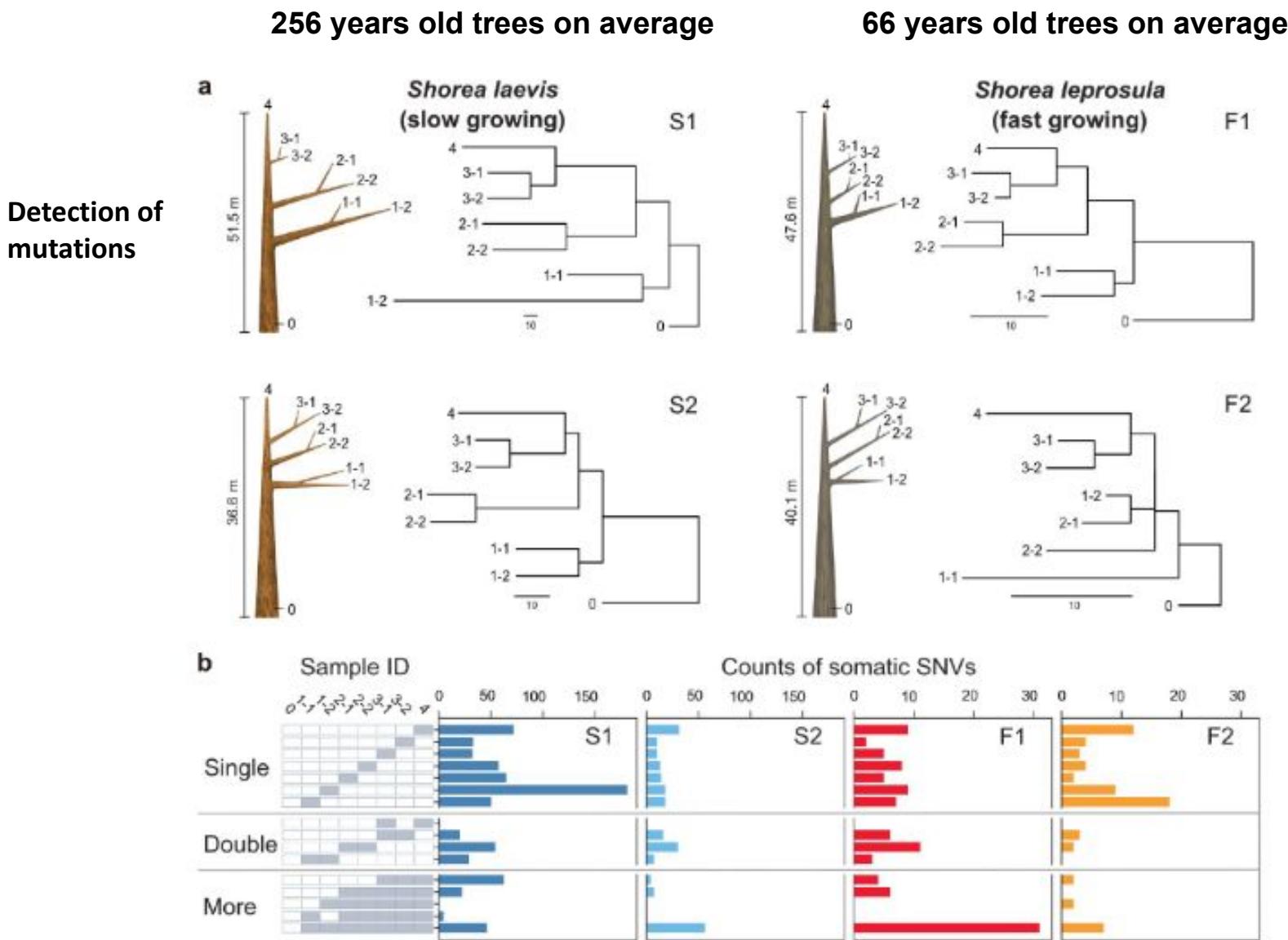
Mutation accumulate along plant growth

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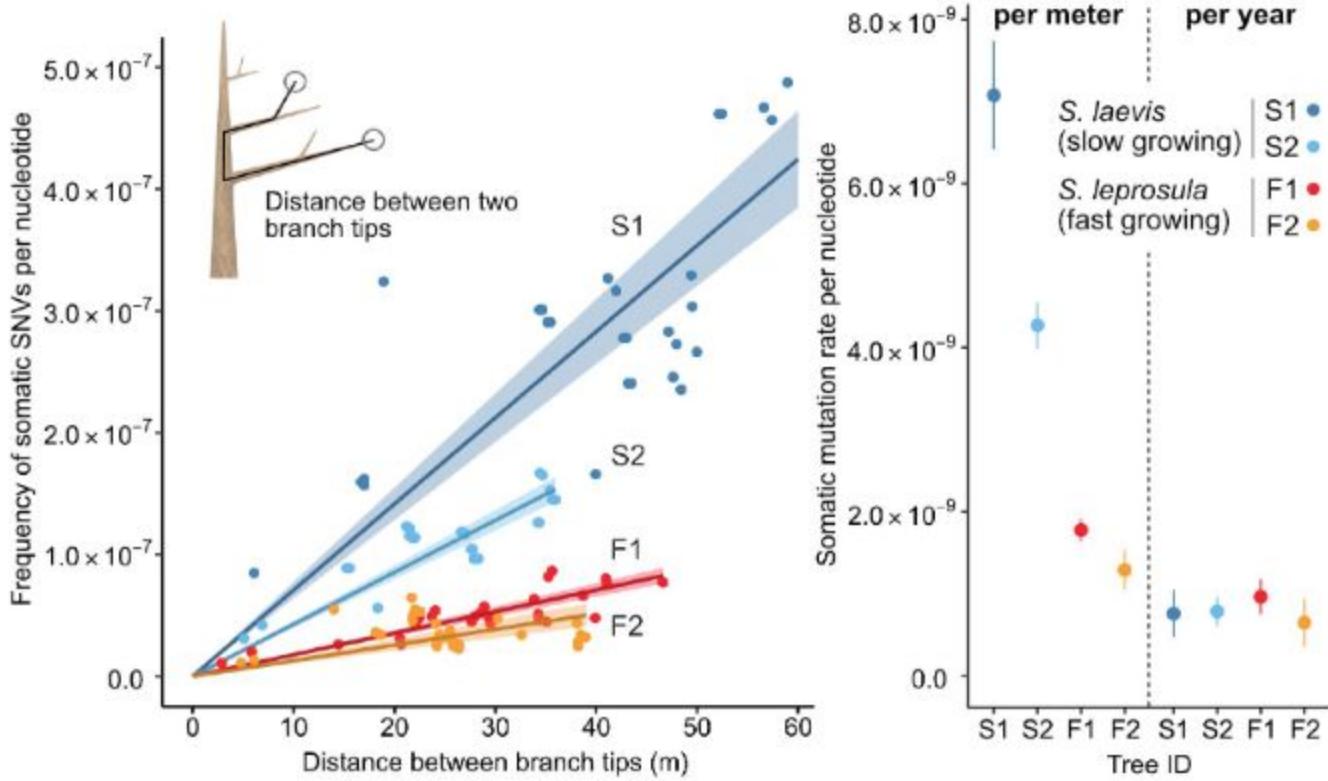
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Mutation accumulate along growth: an effect of the cell divisions or the DNA repair?



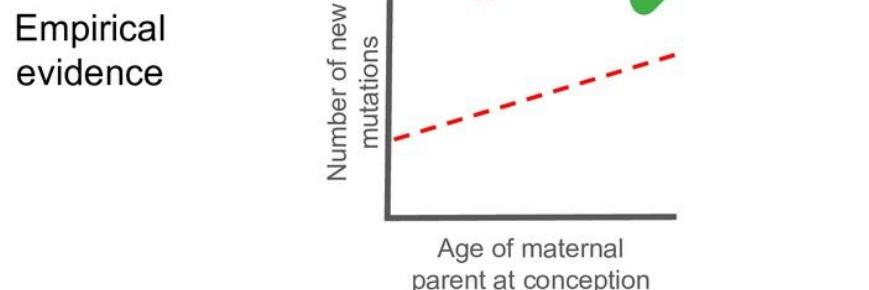
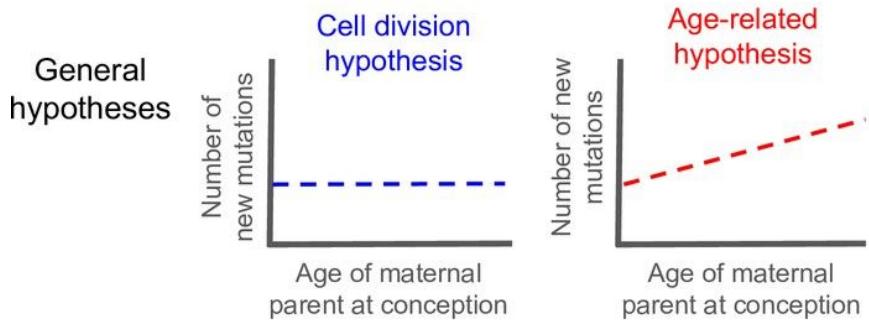
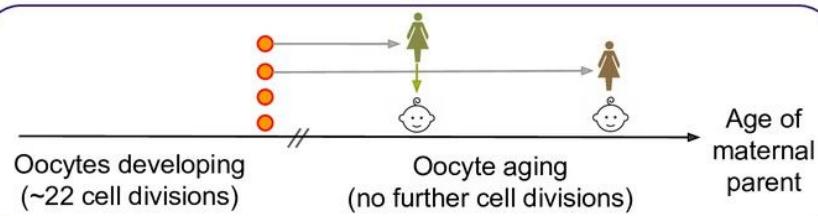
Mutation accumulate along growth: an effect of the cell divisions or the DNA repair?



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

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

Animals



Plants

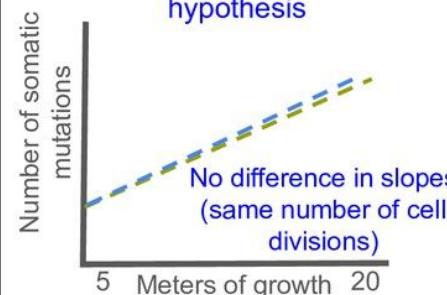
Slow-growing tree species (~250 years old)



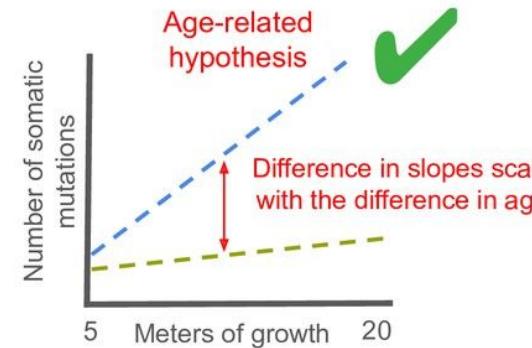
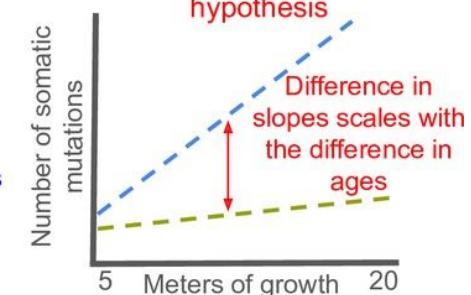
Fast-growing tree species (~70 years old)



Cell division hypothesis



Age-related hypothesis

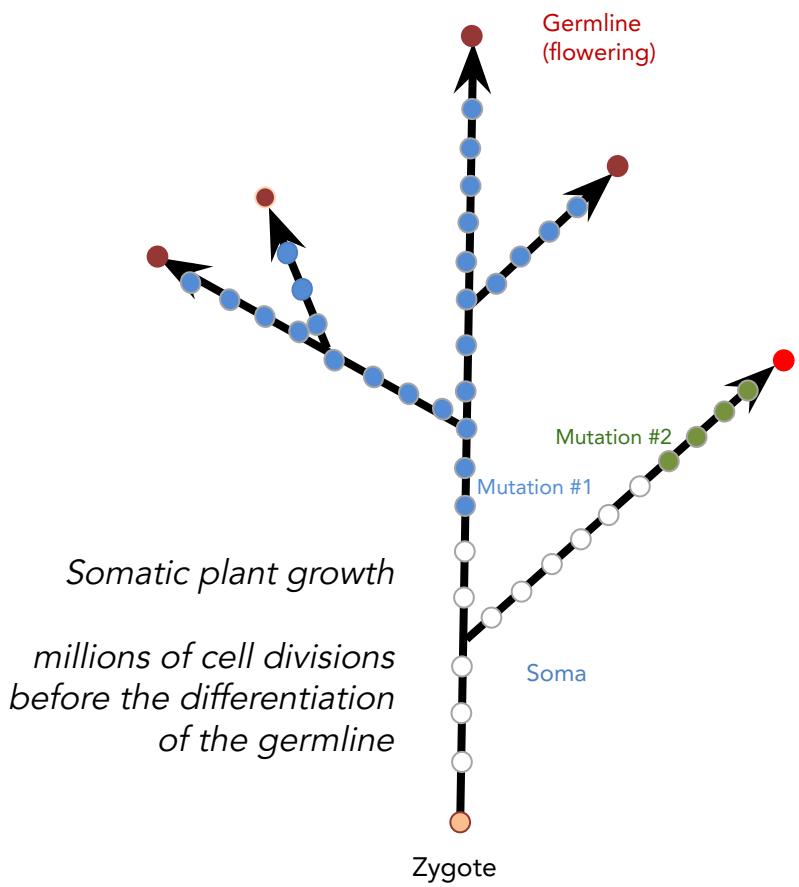


Leroy 2023, eLife

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



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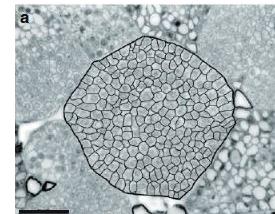
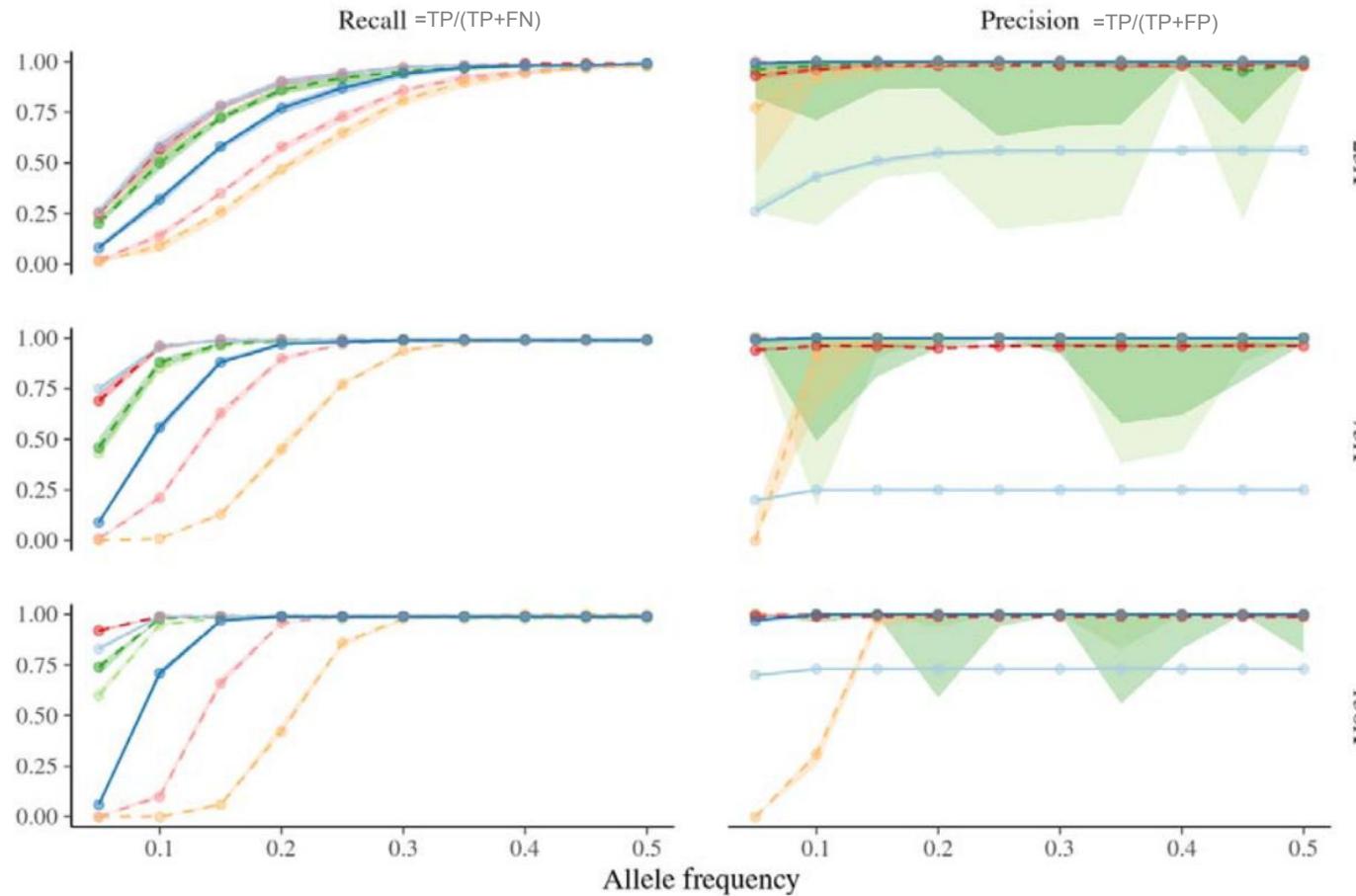
→ Does this vary depending on the tissues?
Are mutations generated by DNA replication or DNA repair errors?

Somatic mutation can be passed to the progeny in plants

→ Does this apply to all plants?

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



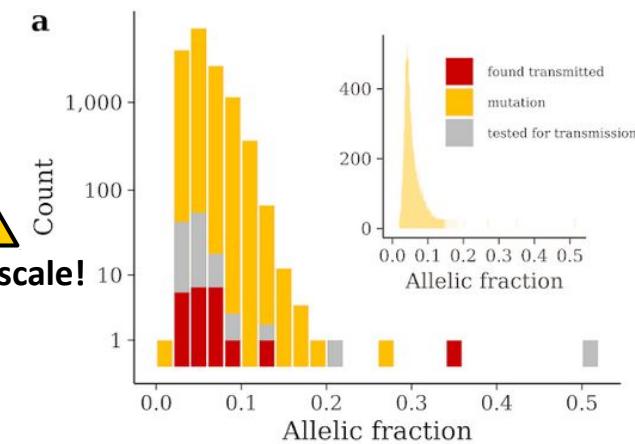
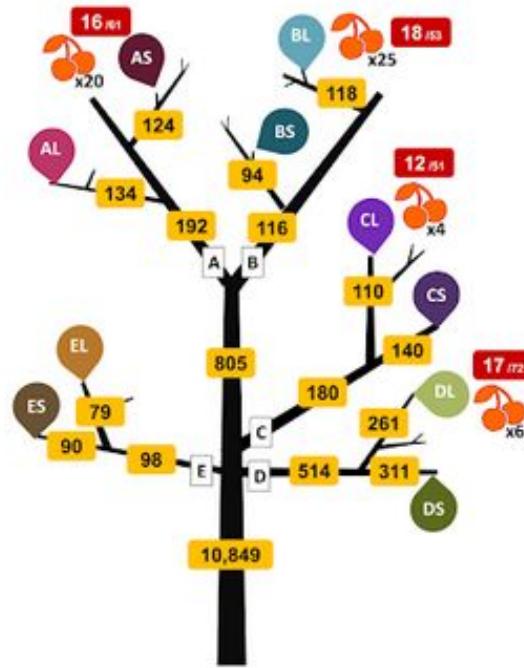
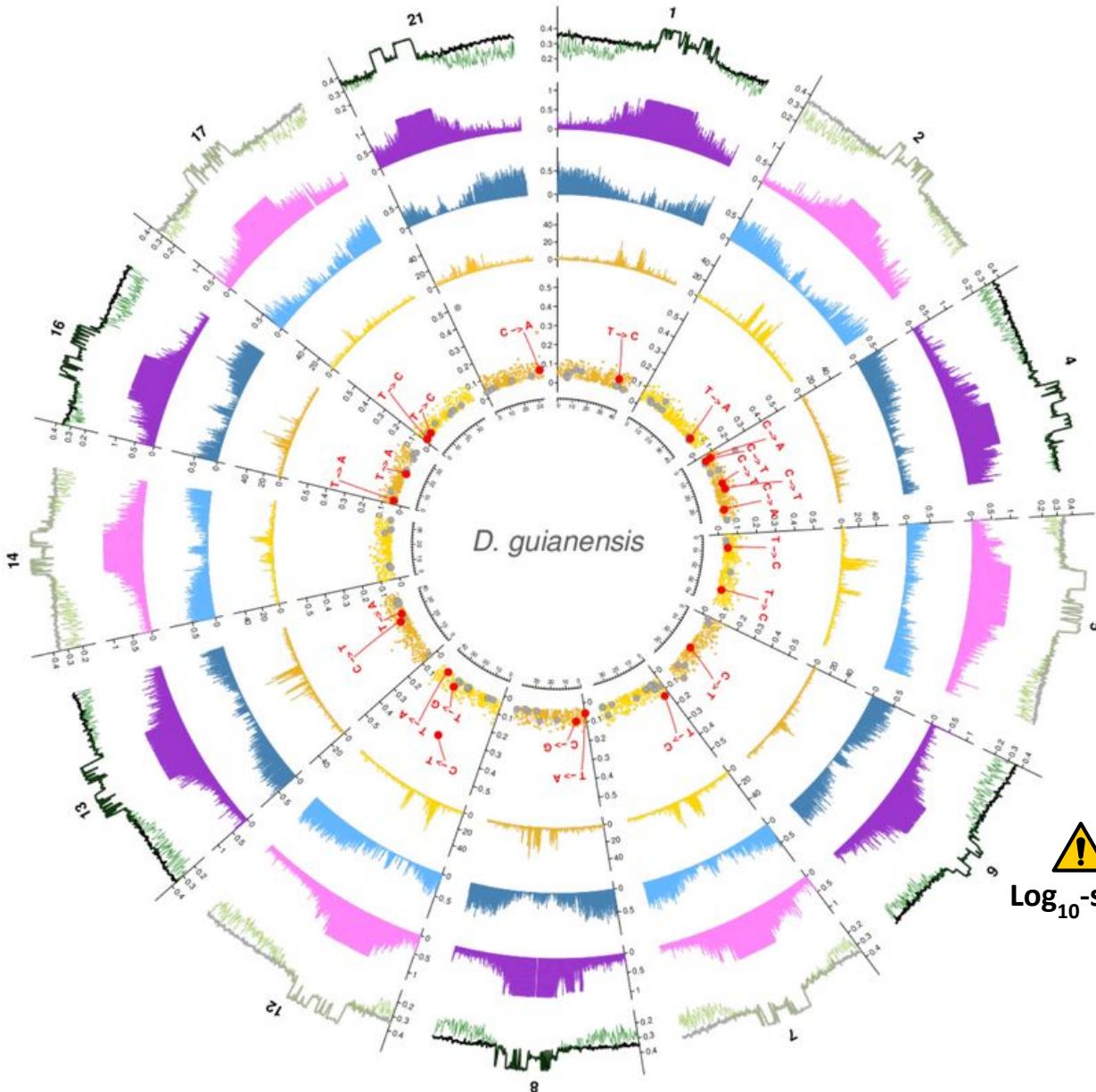
Myriam Heuertz



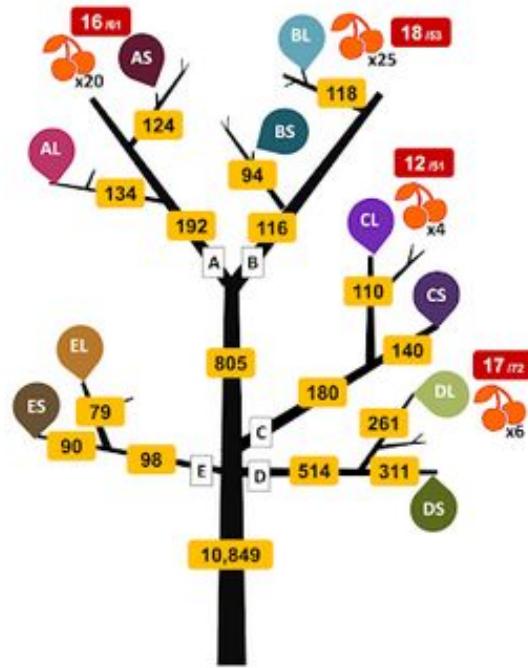
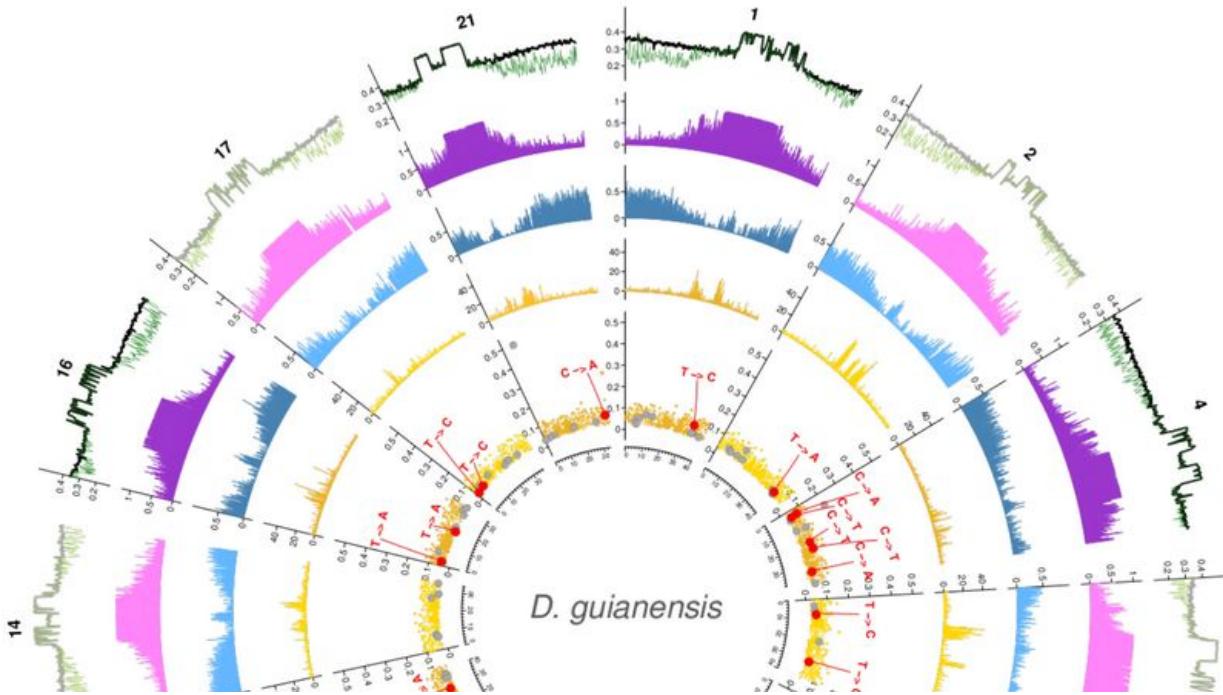
Niklas Tysklind

freebayes	MuSE	Somatic Sniper	VarScan	- - Cancer variant caller
GATK	Mutect2	Strelka2		— Generic caller

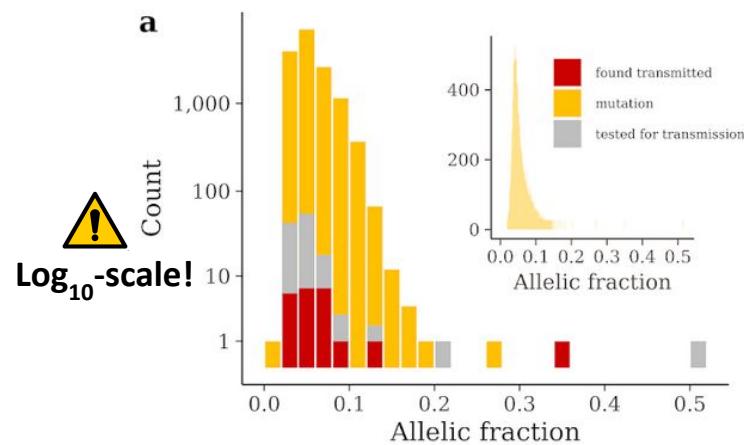
So if it is theoretically possible to identify low freq mutations, at which allele frequency new mutations are observed?



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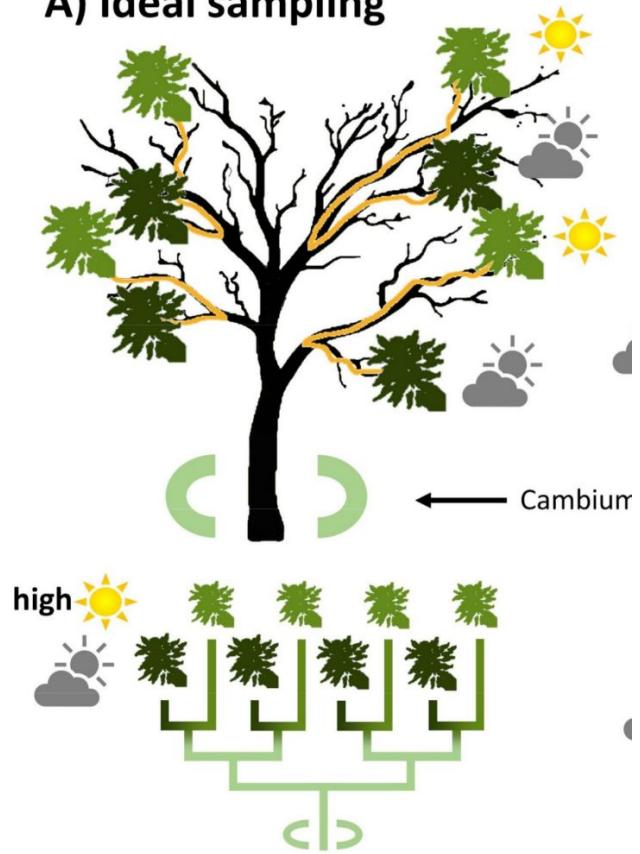


The vast majority of de novo plant mutations are at low allele frequency within the plant and are therefore difficult to detect, but they can be evolutionary important, since these mutations can also be transmitted to the next generation!

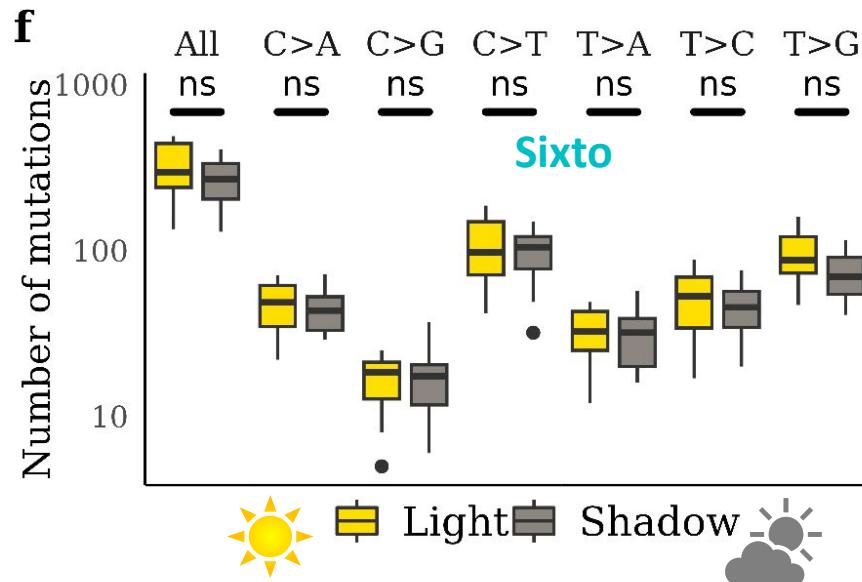
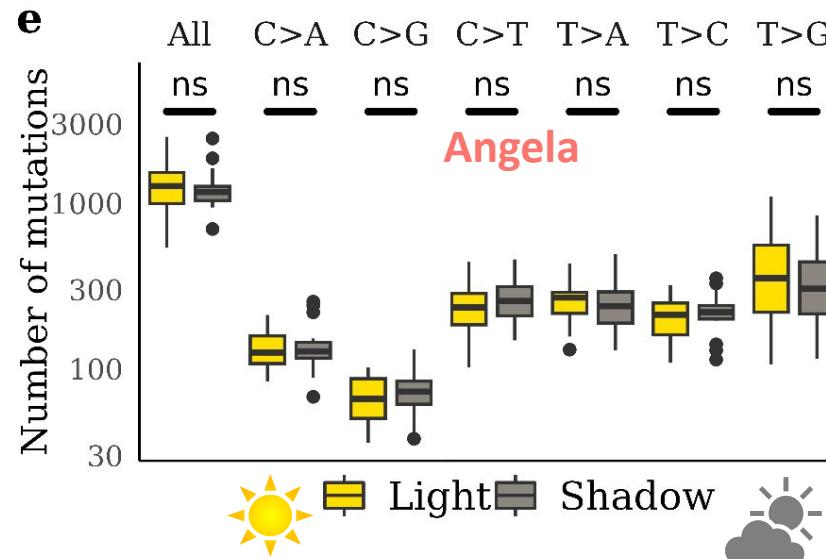


Are mutations UV-induced in trees?

A) Ideal sampling



Mutations are not more common in sun exposed branches



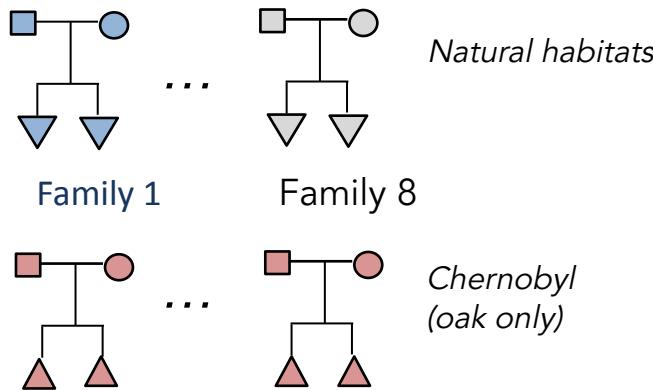
Importance of other mutagens?

Fold-changes in mutation rates corresponding to a single tree generation, over which a major nuclear accident took place.

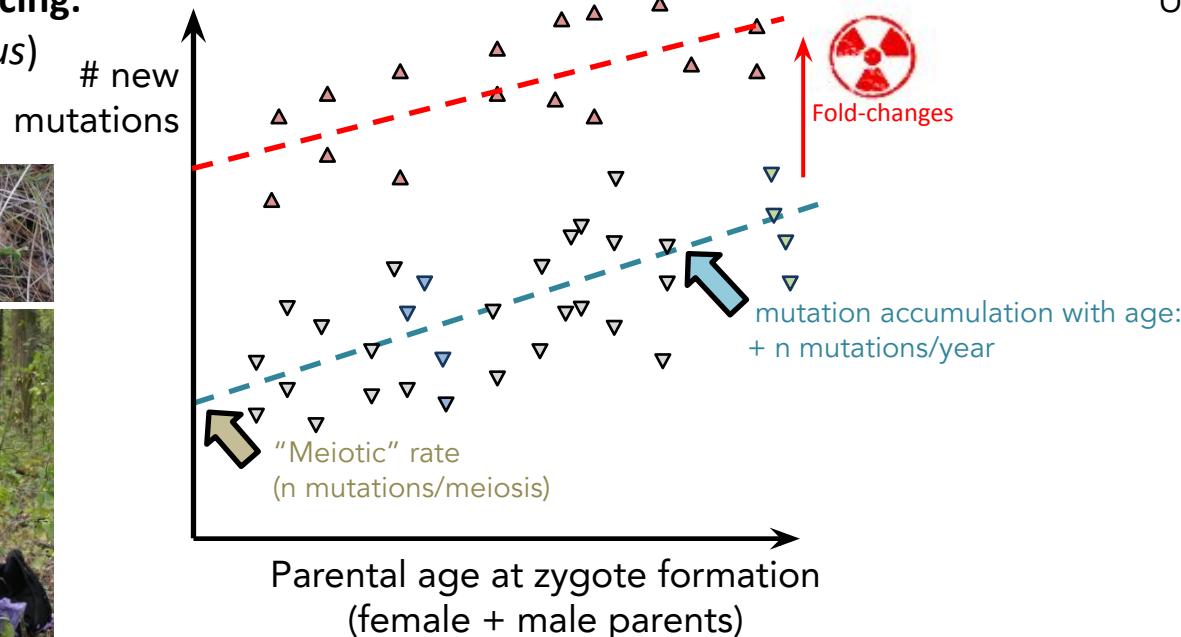
'18 & '20 Marie-Curie
proposal
MutaSHEETER

REJECTED

In situ
parent-progeny
relationships
reconstruction using
DNA markers



**Full genome
trio-sequencing:**
Oak (*Quercus*)



Chernobyl, Sept. 2018



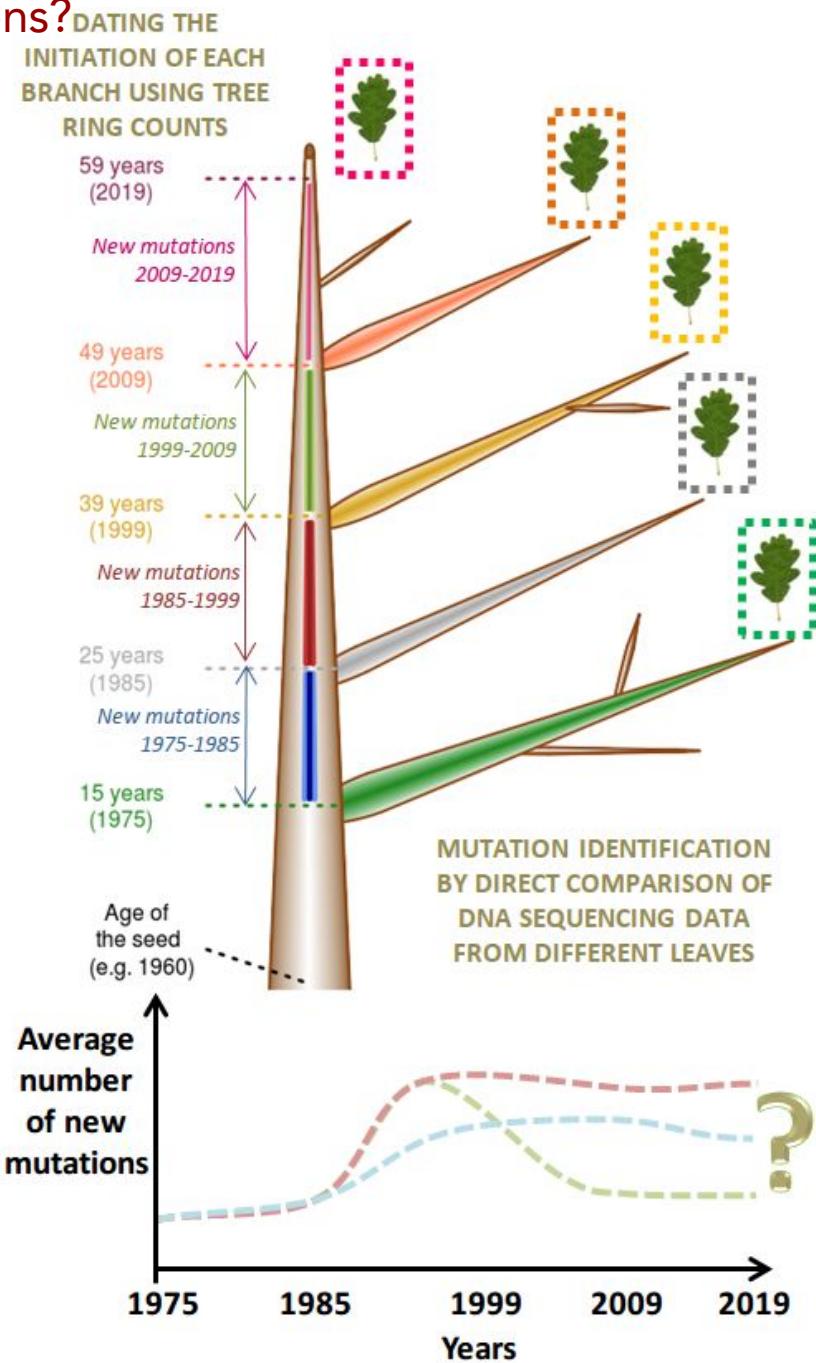
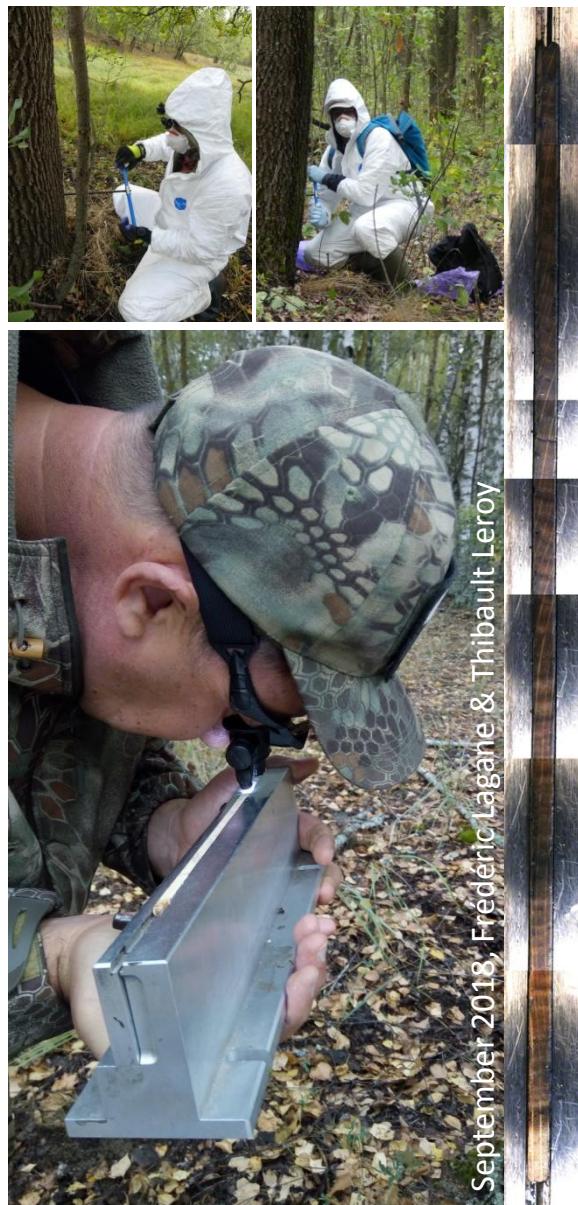
M. Lascoux C. Plomion
Uppsala Bordeaux



T. Mousseau
Univ. South Carolina

Importance of other mutagens?

Chernobyl forests (< 5km Chernobyl NPP)



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

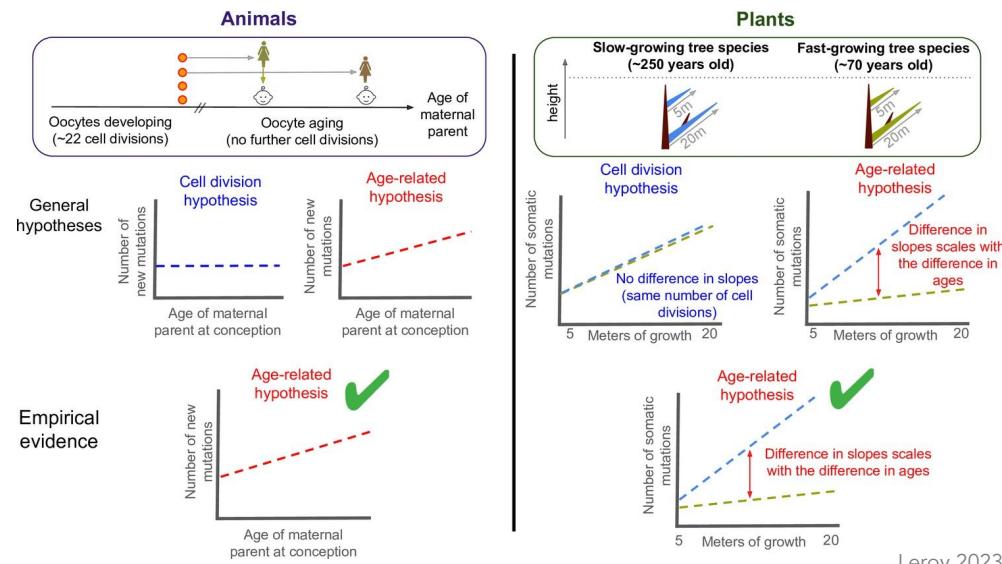
The per-generation heritable mutation rate: importance for genetic diversity ($4Ne\mu$) and divergence (molecular clock)

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)



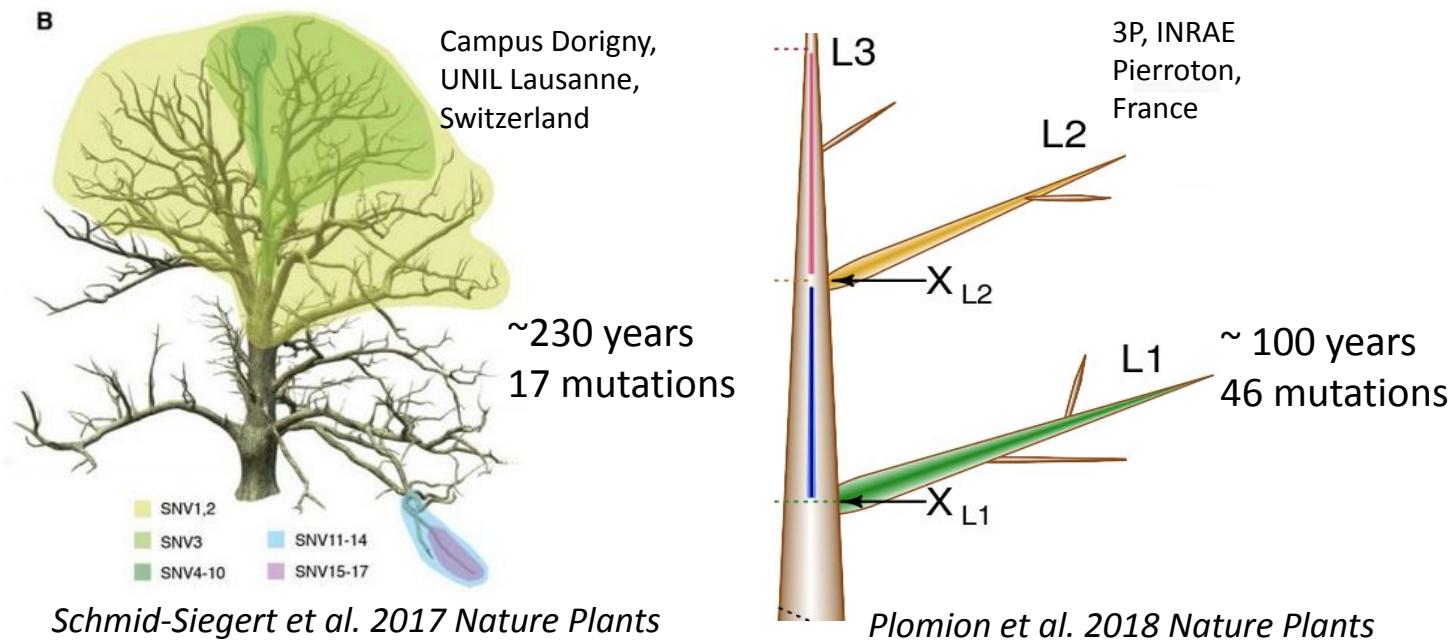
« The Major Oak », Sherwood Forest, Nottinghamshire, England (800-1,000 years old, UK's most visited tree)



Thibault Leroy

thibault.leroy@inrae.fr
 / / : @TiBoLeroyInEn
<https://thibaultleroyfr.github.io>

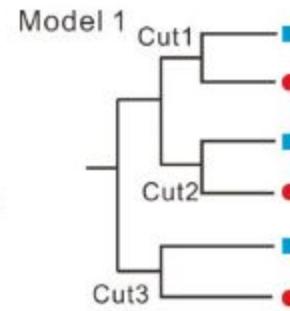
First empirical evidences: “Napoleome” oak tree in Lausanne



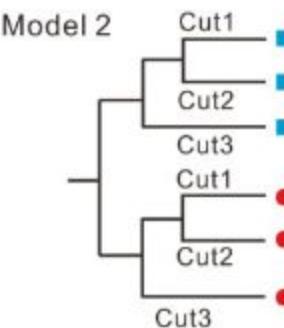
Some mutations indeed occur along growth

Apparent paradox however:
2.7x less mutations in the 2.3x older tree!

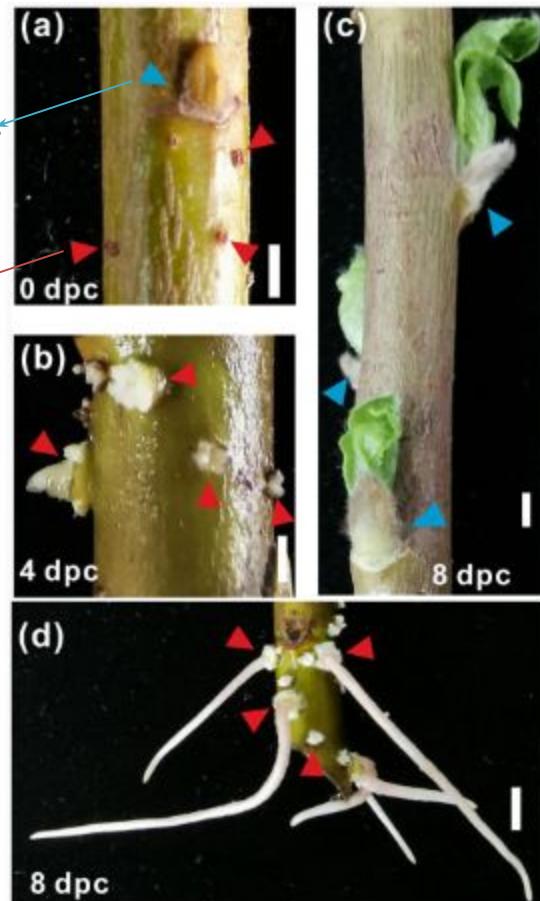
Late segregation ('plant model')



Early segregation ('animal model')



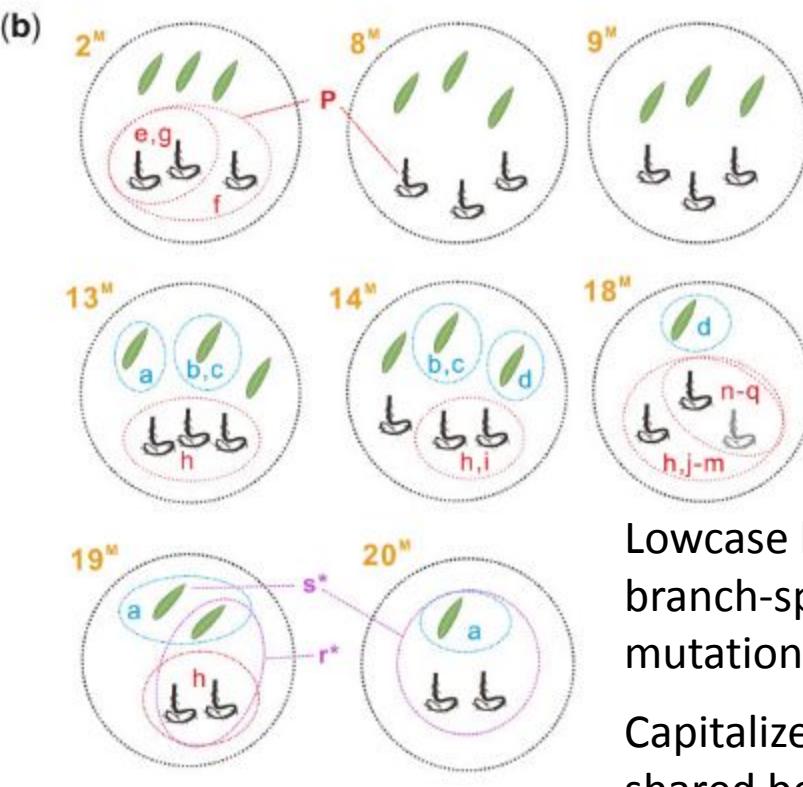
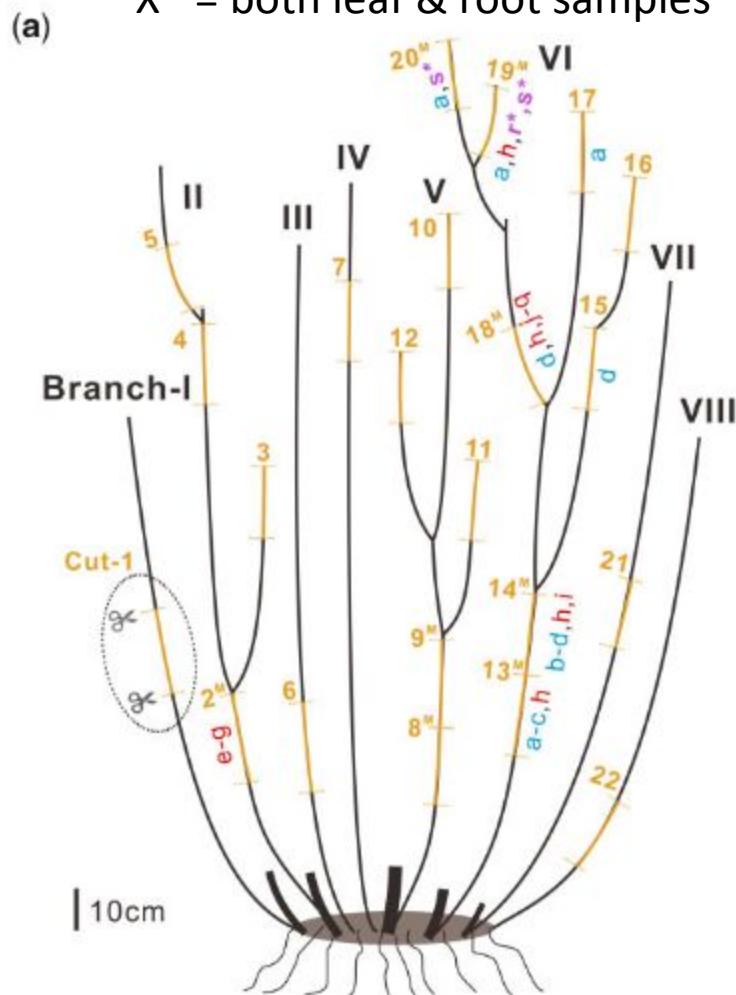
Latest progenitor cells:
■ Leaf
● Adventitious root



WGS of 33 leaves and 22 adventitious roots (>2000 X in total)

X = sample ID

X^M = both leaf & root samples



Lowcase letters:
branch-specific
mutation (BR-s)

Capitalized letters:
shared between
different branches
(BR-m, only "P"
here)



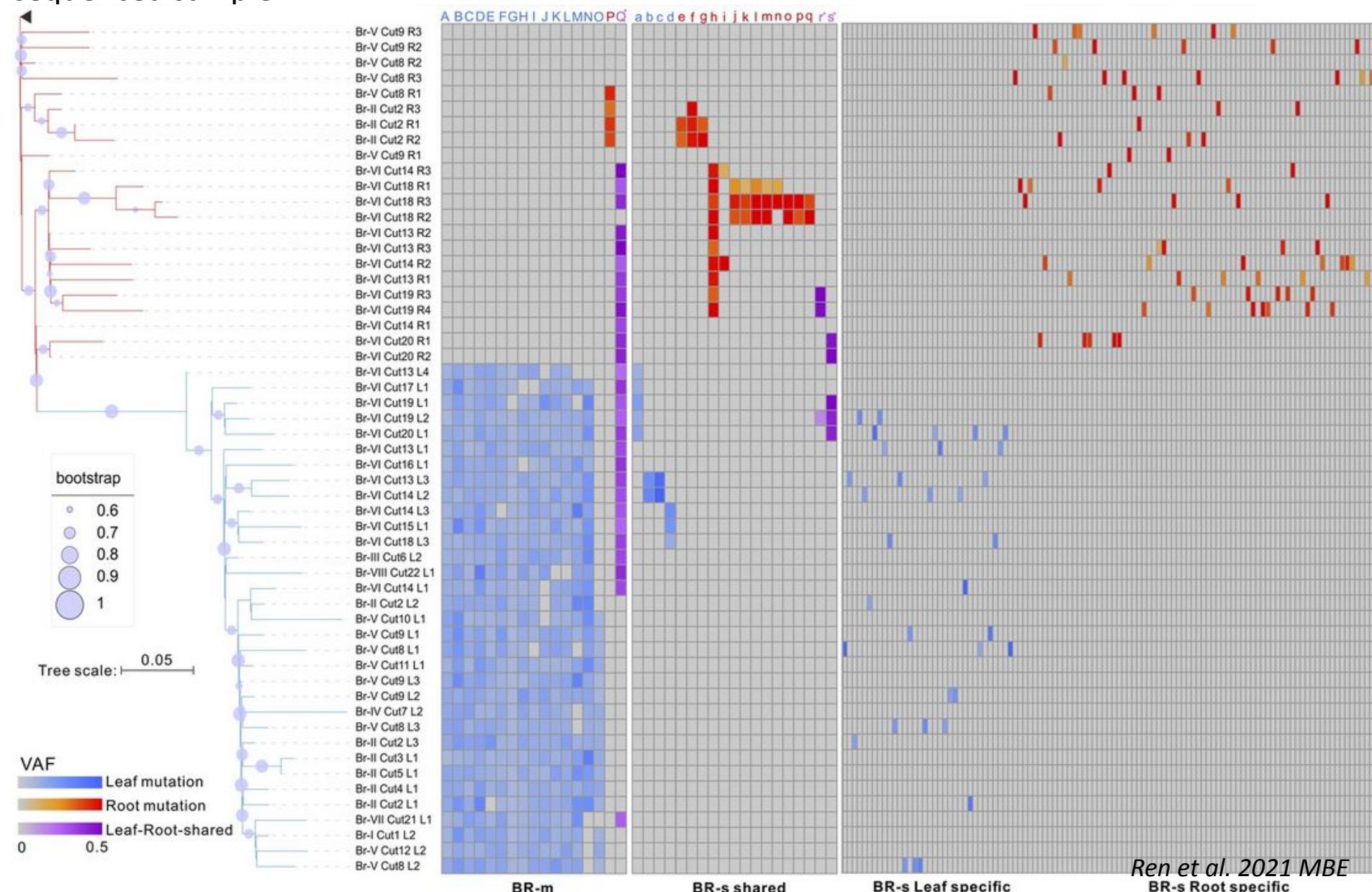
In total: 199 reliable somatic mutations: 182 BR-s and 17 BR-m

Among the 8 X^M : 108 including 35 leaf mutations and 73 root mutations (again more on roots, but here a limit to conclude due to the callus formation step)

Ren et al. 2021 MBE

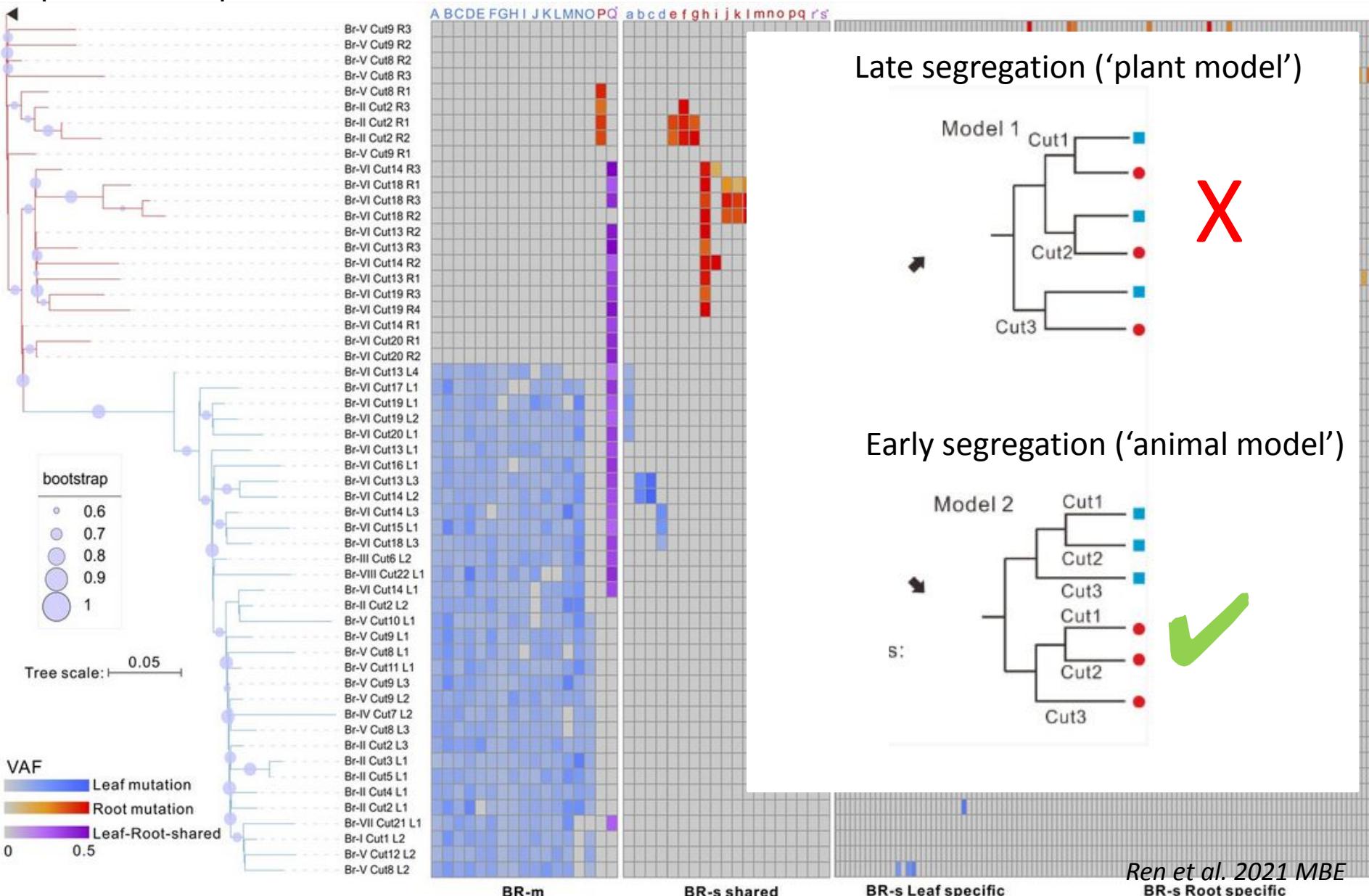
Tracking of mutations in all samples

17 BR-m (“A~Q”), 19 BR-s shared (“a~s”), and 108 BR-s sample-specific mutations in each sequenced sample



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Ren et al. 2021 MBE
BR-s Root specific

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

(A) Late segregation, late differentiation



(B) Early segregation, late differentiation



(C) Early segregation, early differentiation



- G Segregated germline cell lineage
- Undifferentiated stem cell
- Differentiated somatic cell
- Differentiated germline cell

[...] 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”

Summary: Existing knowledge on plant mutation rates (almost all)

- Somatic mutations are accumulated along growth (widely supported empirically)
- Cancer-derived methods are more robust to identify these variants
- 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?)



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

?

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