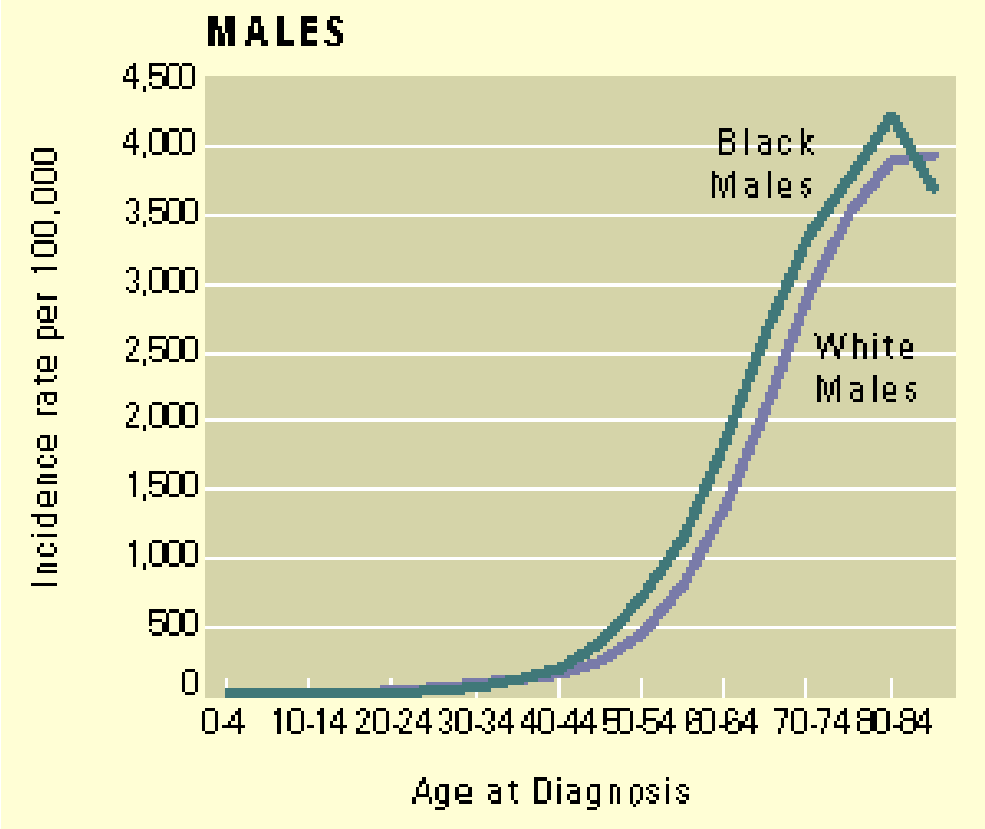
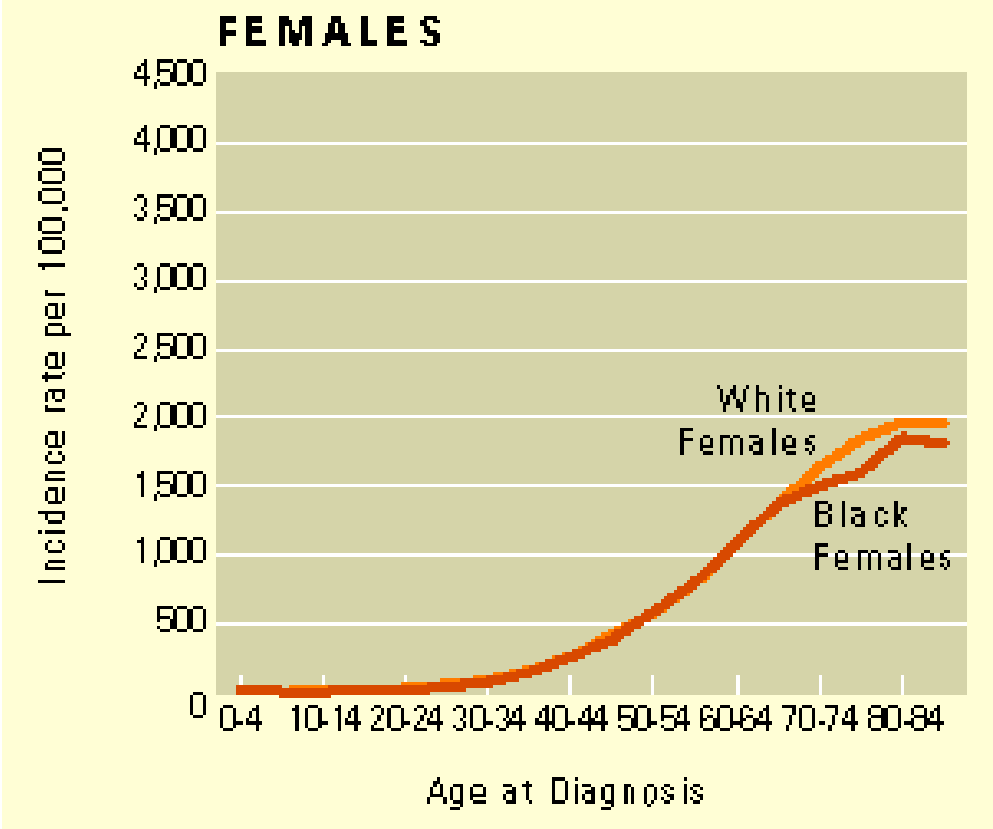
Age is the greatest carcinogen

ACS pamphlet

Age & Cancer

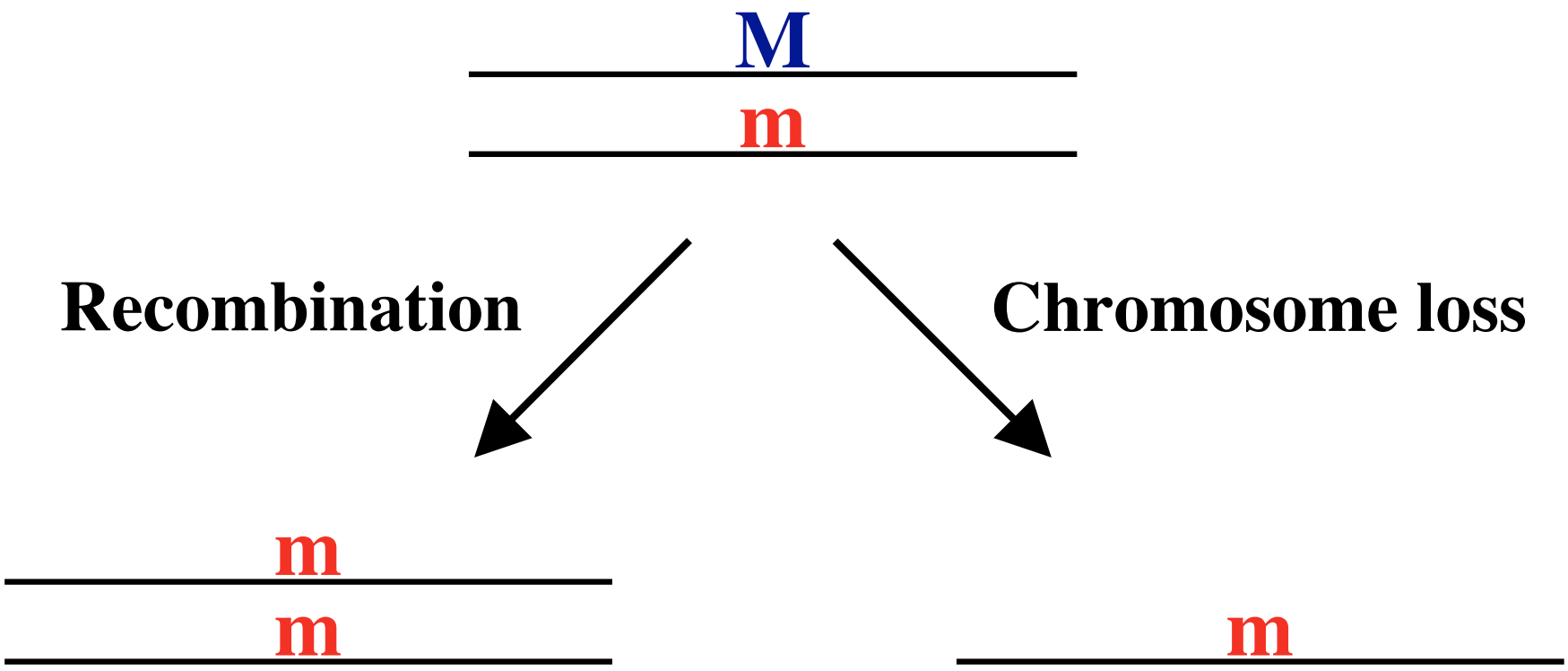




Source: SEER Program, NCI

Michael McMurray

Loss of Heterozygosity

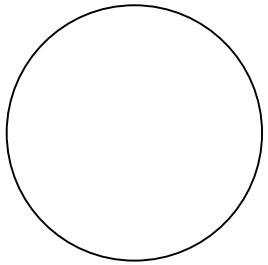


Color Assays for LOH

MET15/met15 ---> **met15/met15**

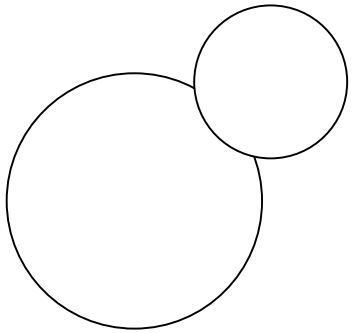
ADE2/ade2 ---> **ade2/ade2**

Pedigree Analysis of Aging Yeast Cells



Mother

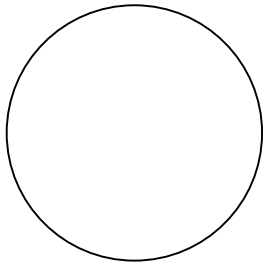
Pedigree Analysis of Aging Yeast Cells



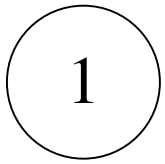
daughter

Mother

Pedigree Analysis of Aging Yeast Cells

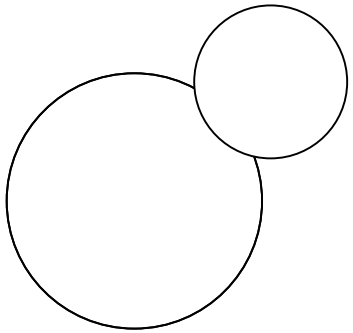


Mother



daughter

Pedigree Analysis of Aging Yeast Cells



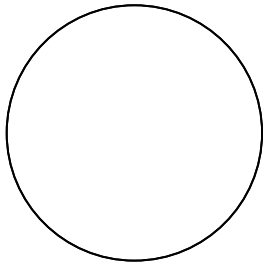
daughter

Mother

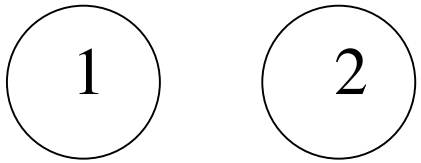
1

daughter

Pedigree Analysis of Aging Yeast Cells

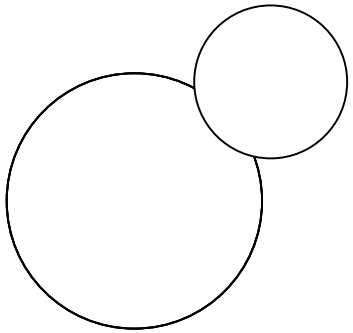


Mother



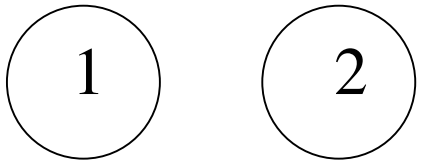
daughters

Pedigree Analysis of Aging Yeast Cells



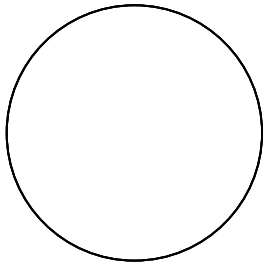
daughter

Mother

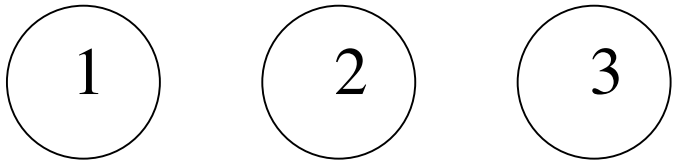


daughters

Pedigree Analysis of Aging Yeast Cells

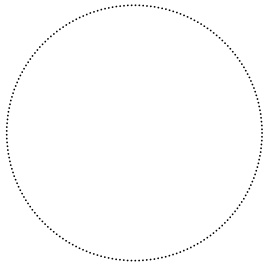


Mother



daughters

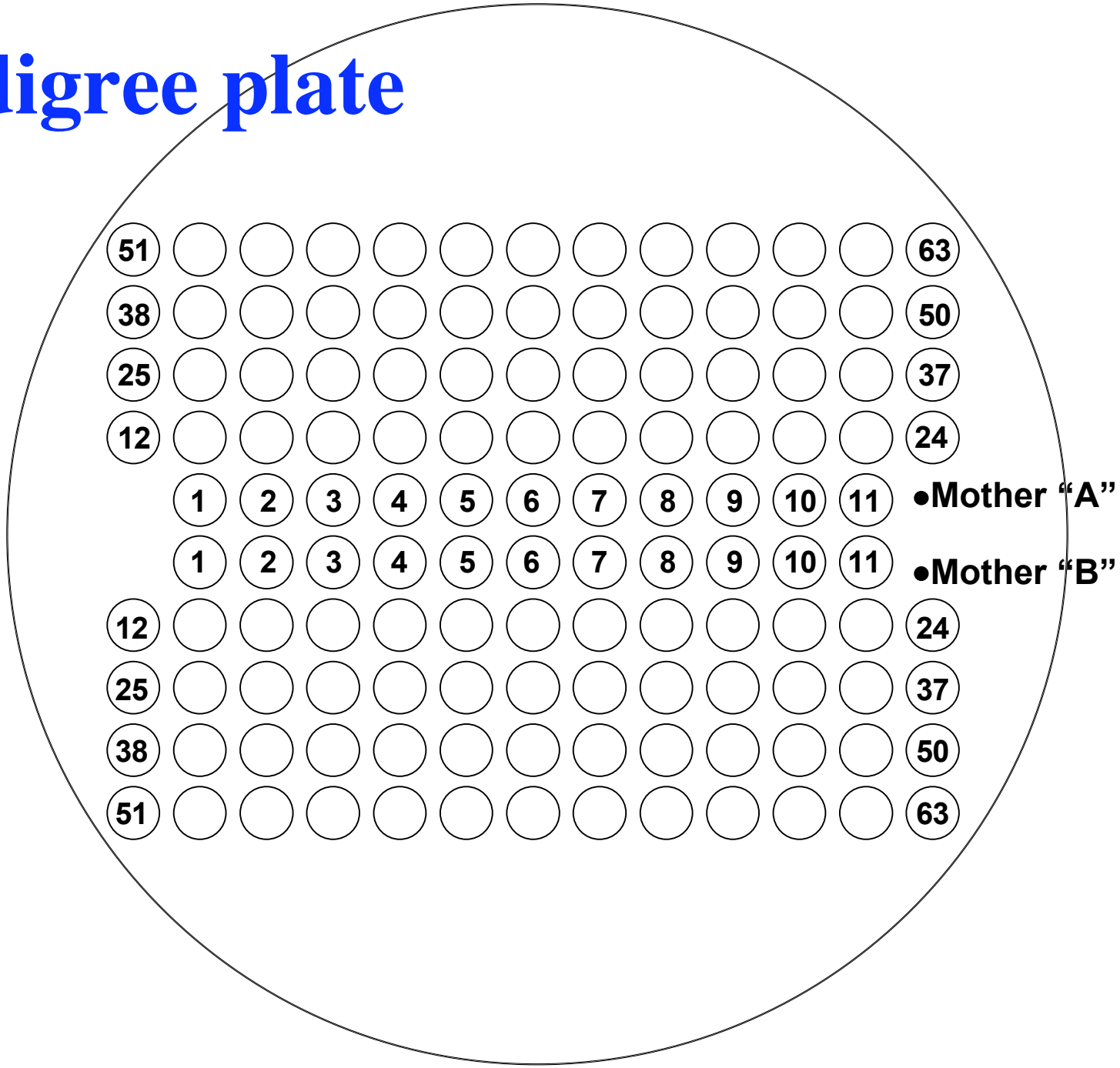
Pedigree Analysis of Aging Yeast Cells



Mother (dead)

daughters

Pedigree plate

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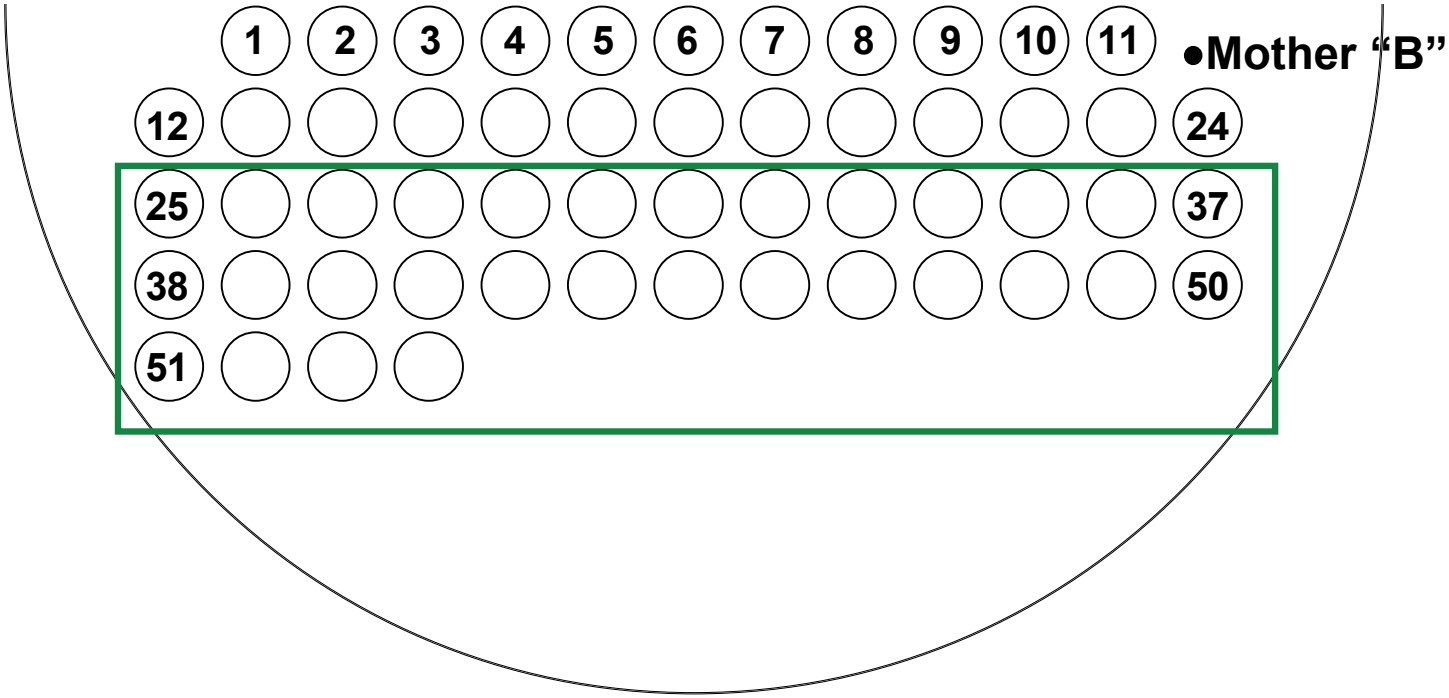
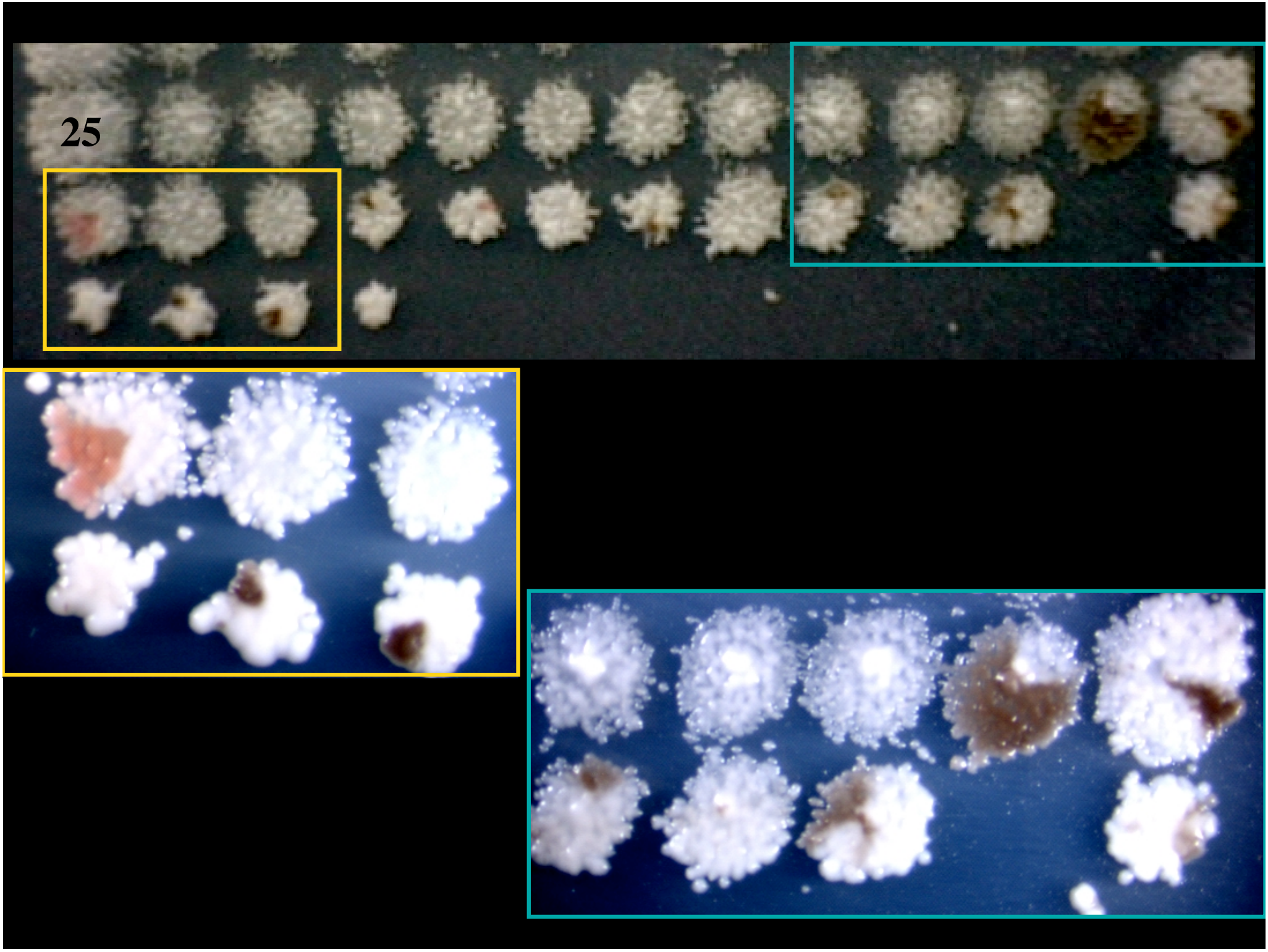
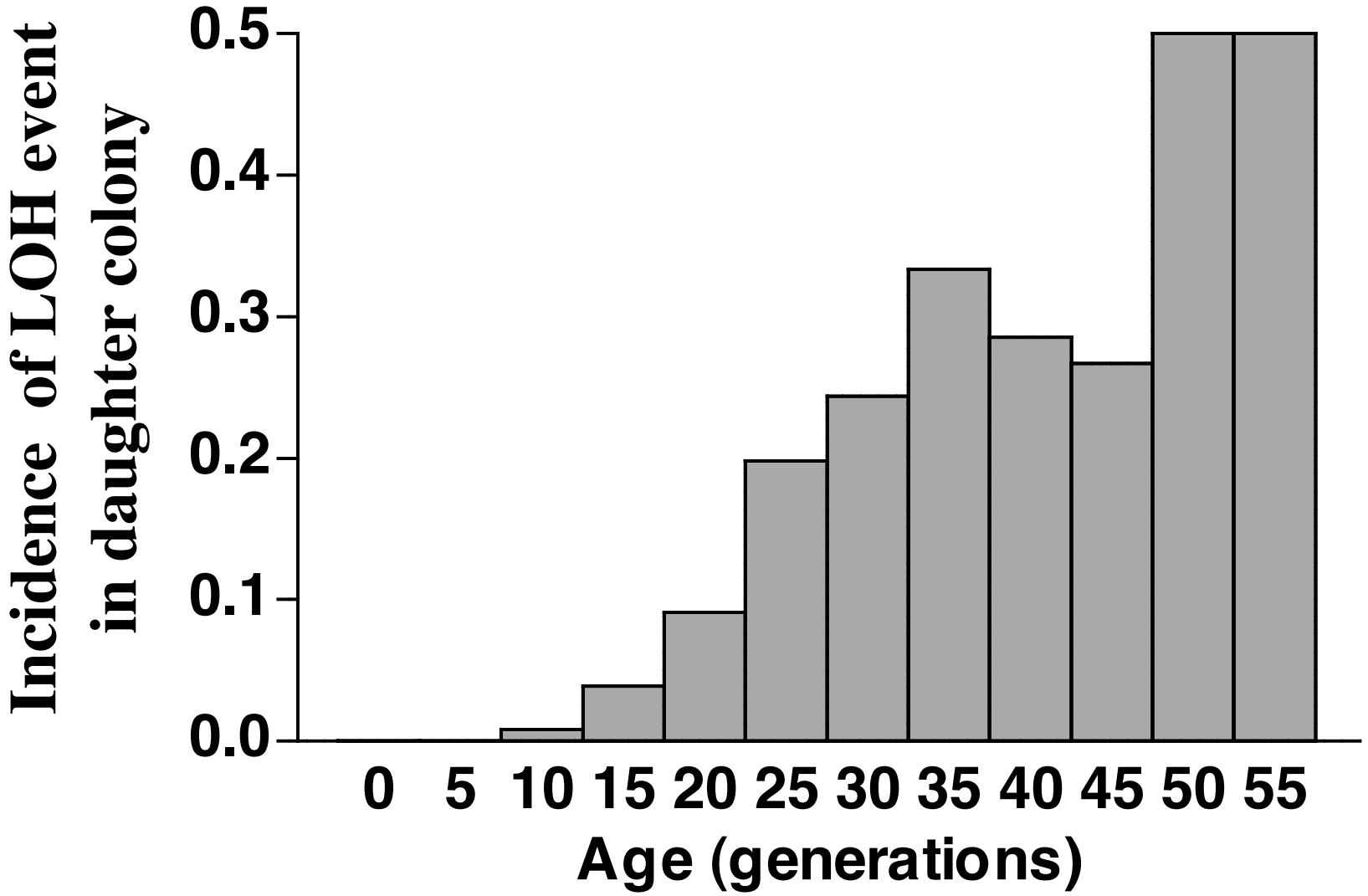
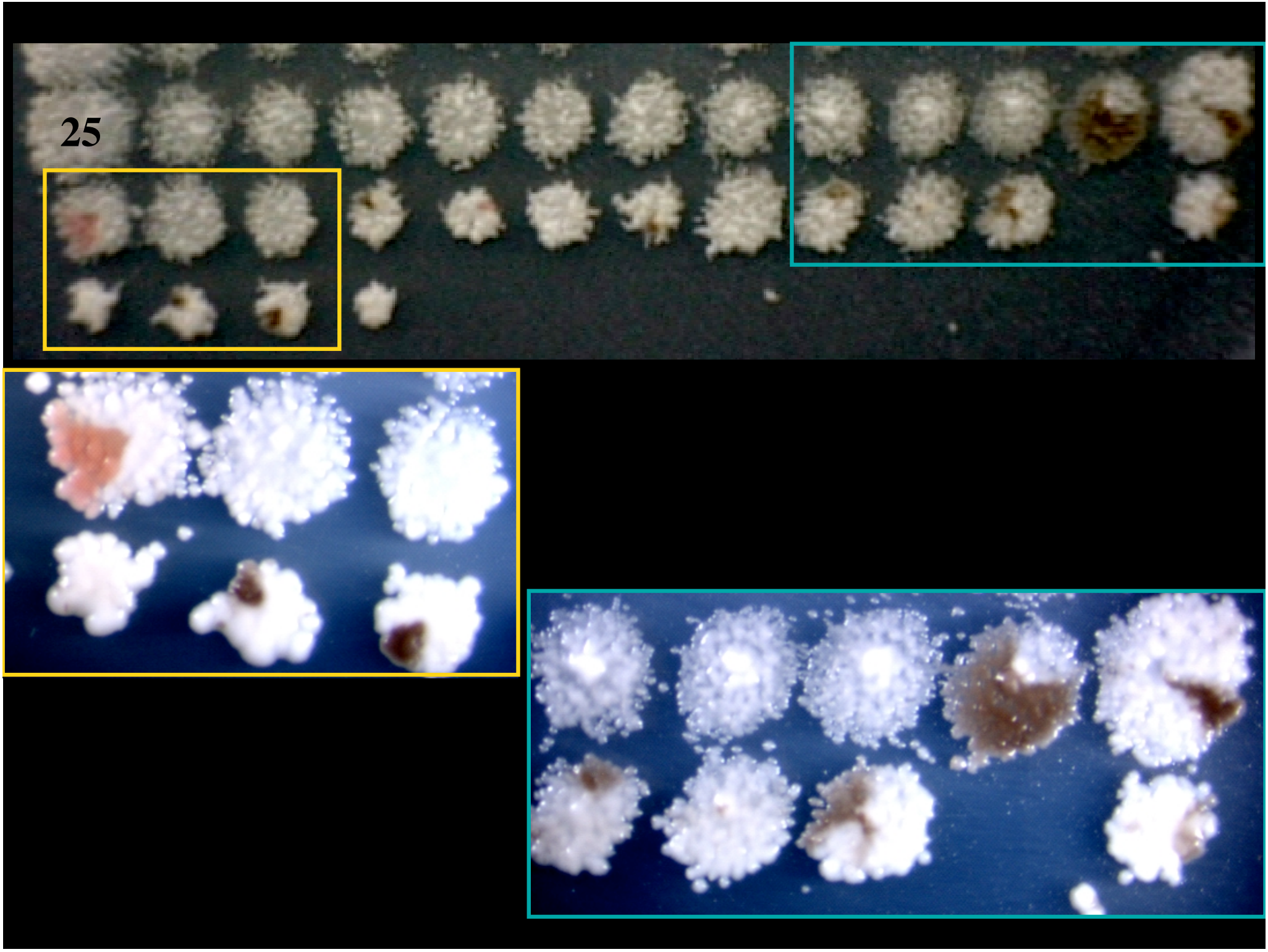

1
2
3
4
5
6
7
8
9
10
11
•Mother "B"
12
24
25
37
38
50
51


25

LOH increases dramatically with the mother cell's age

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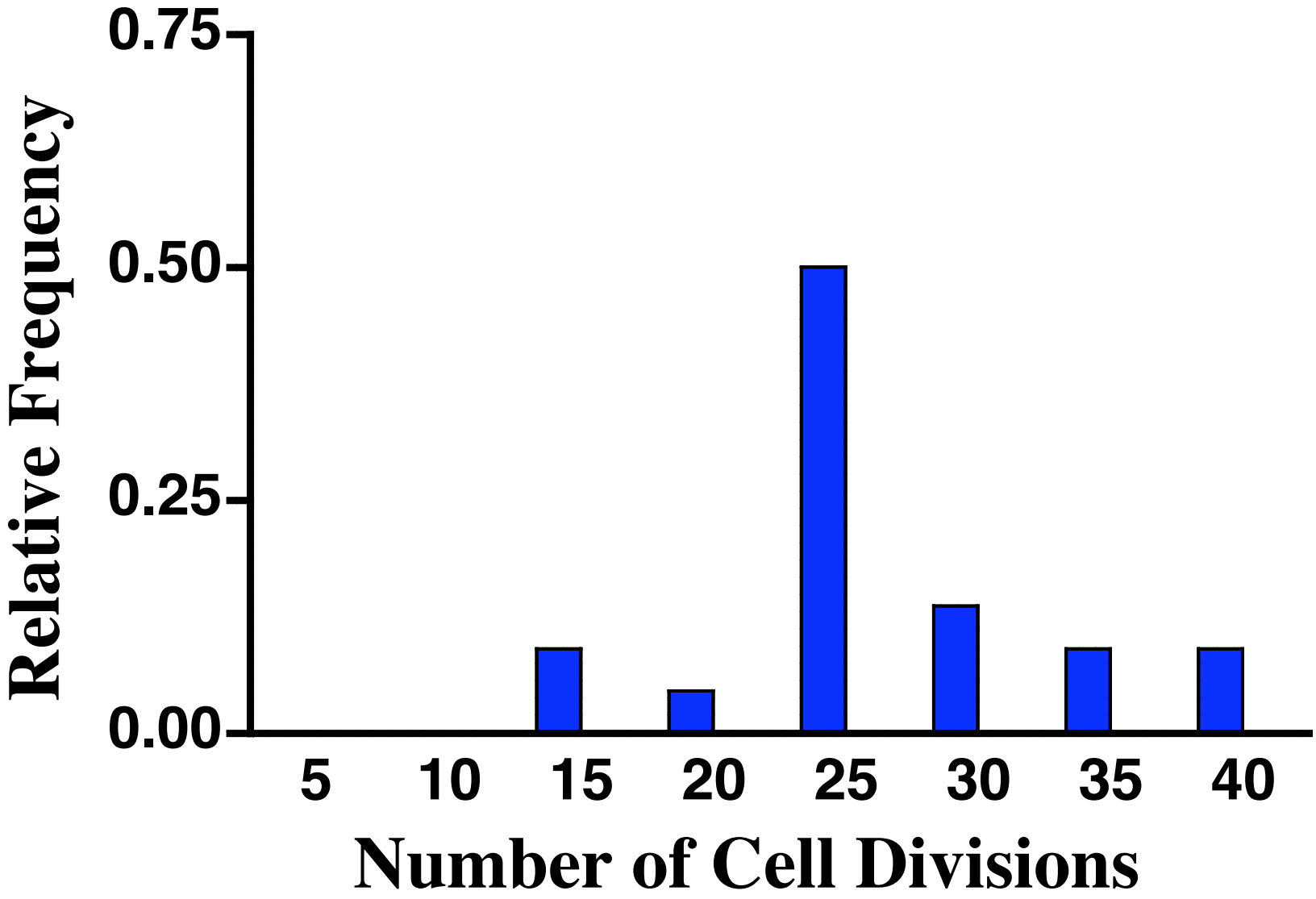
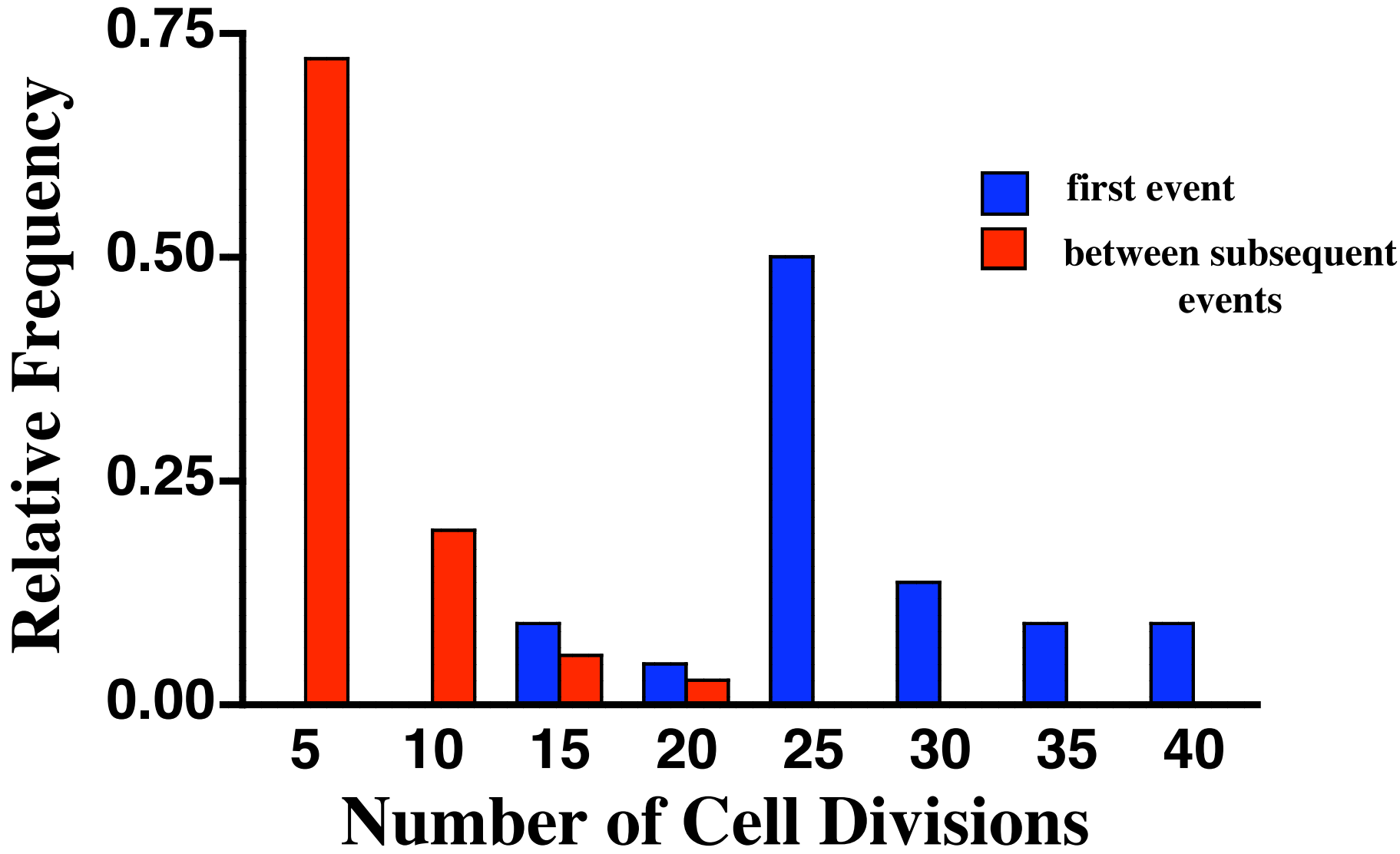
The first *MET15* LOH event has a late onset with age



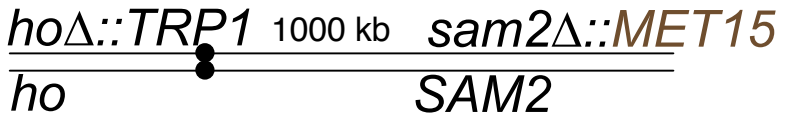
LOH occurs more frequently after the first event at *MET15*



Age induces an increase in the rate of LOH

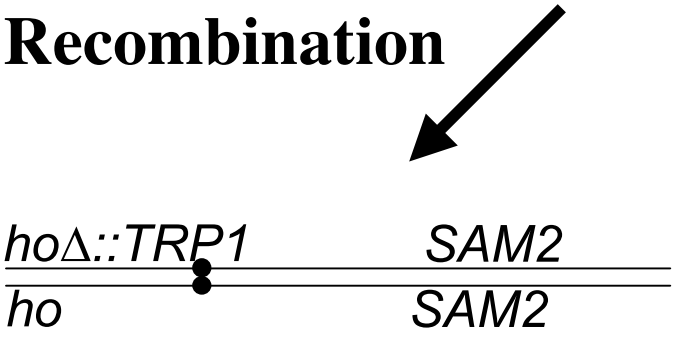
AGE	*MET15* LOH (95% C.I.)	*SAM2* LOH (95% C.I.)
"Young"	7×10^{-4} ($5\text{-}10 \times 10^{-4}$)	1×10^{-4} ($0.5\text{-}2 \times 10^{-4}$)
"Old"	300×10^{-4} ($100\text{-}500 \times 10^{-4}$)	200×10^{-4} ($50\text{-}400 \times 10^{-4}$)

Monitoring LOH at the *SAM2* locus



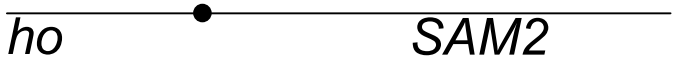
IV

Recombination



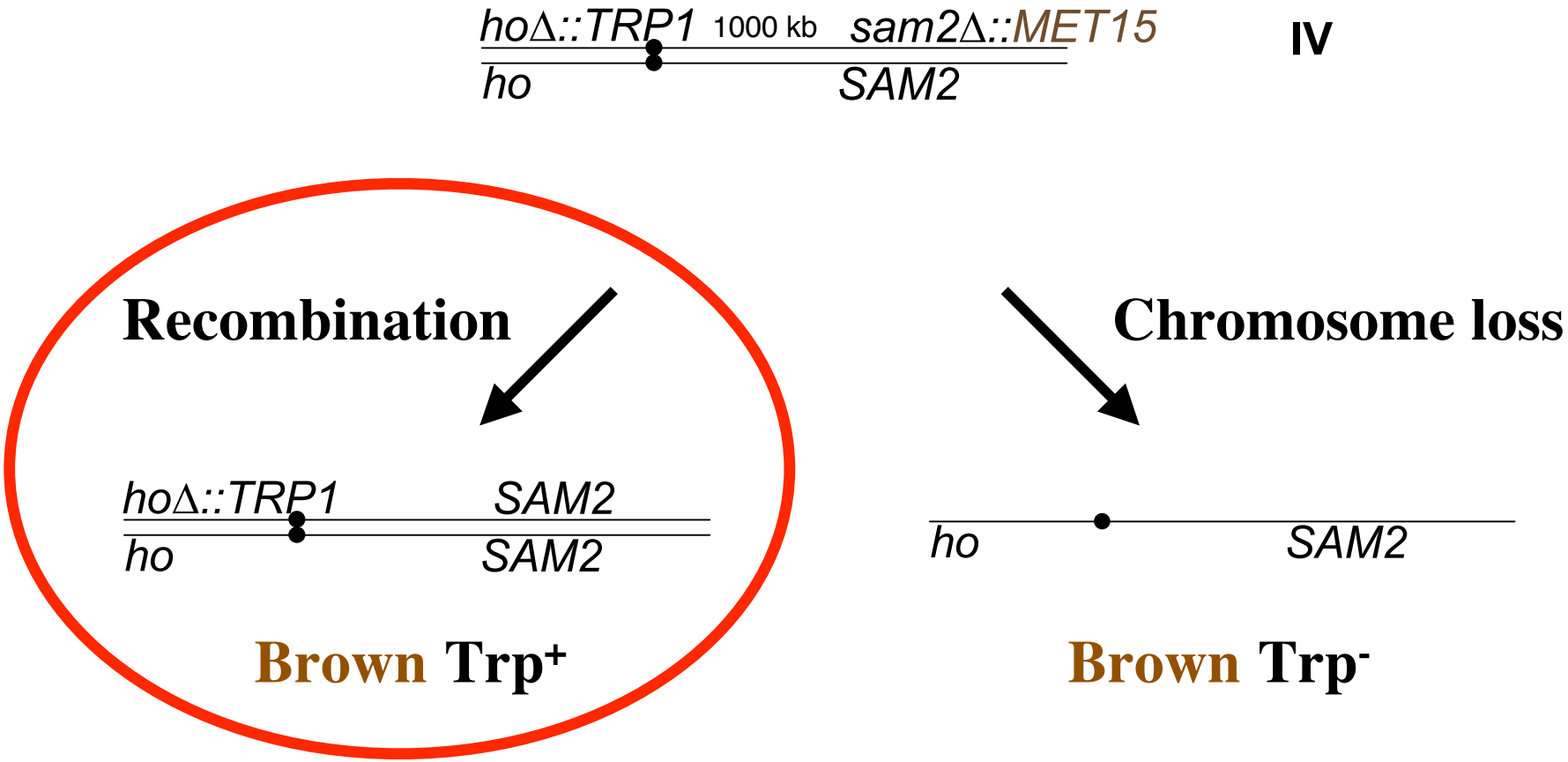
Brown Trp$^+$

Chromosome loss

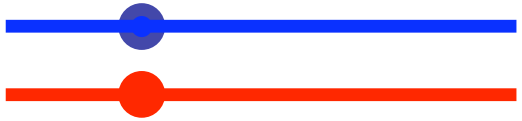


Brown Trp$^-$

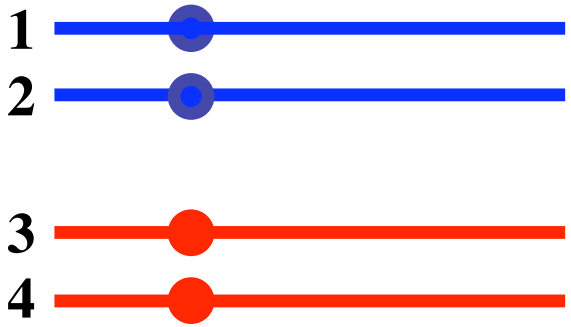
Monitoring LOH at the *SAM2* locus



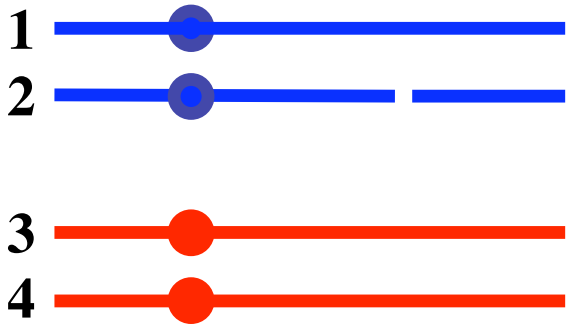
Recombination pathways for LOH



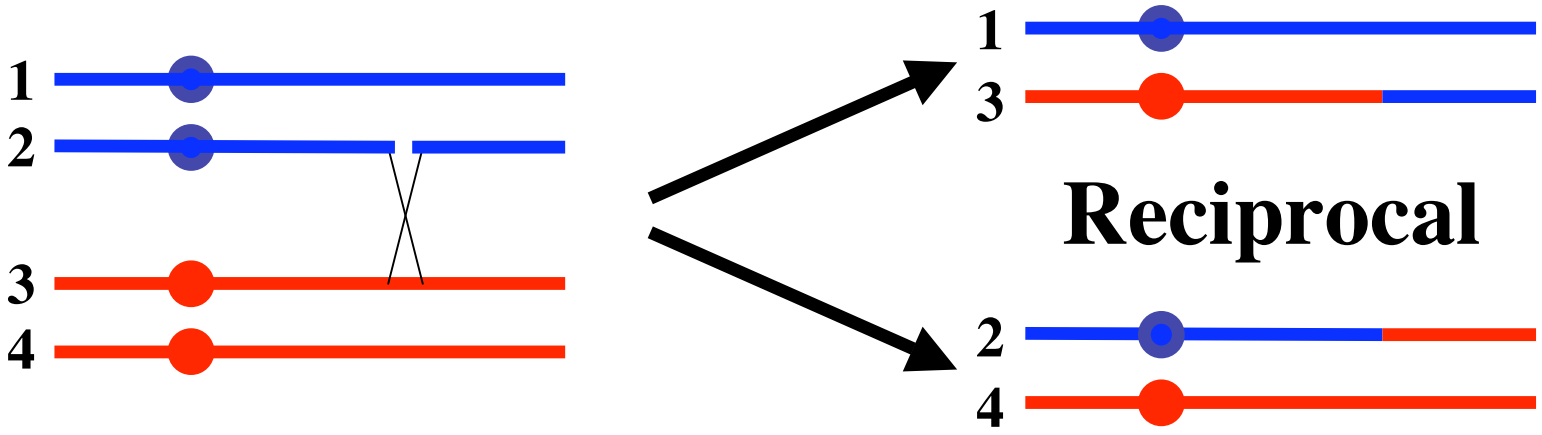
Recombination pathways for LOH



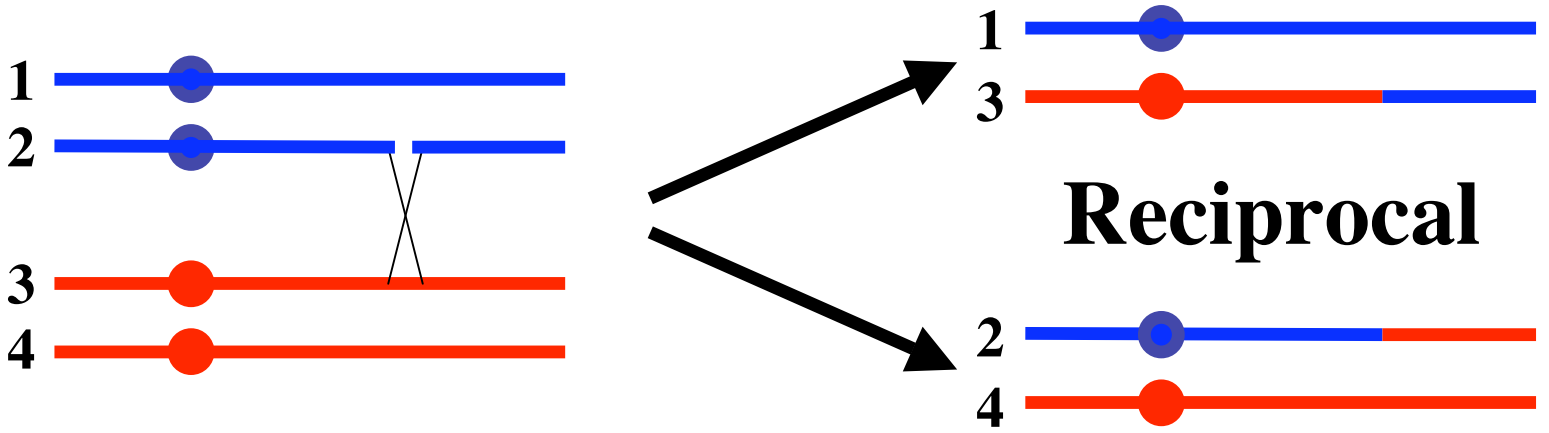
Recombination pathways for LOH

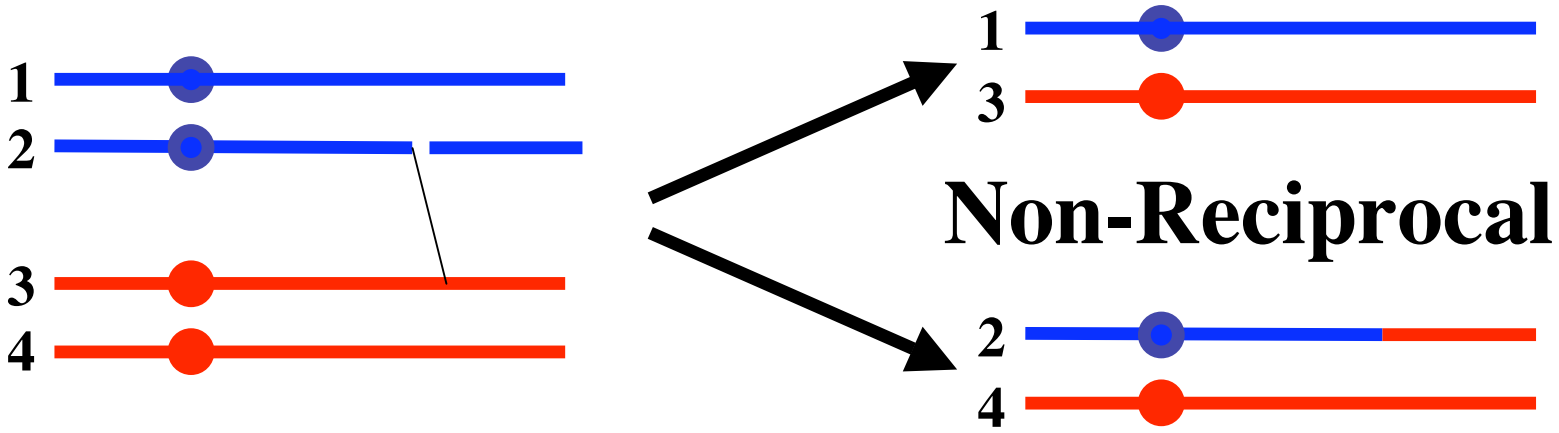


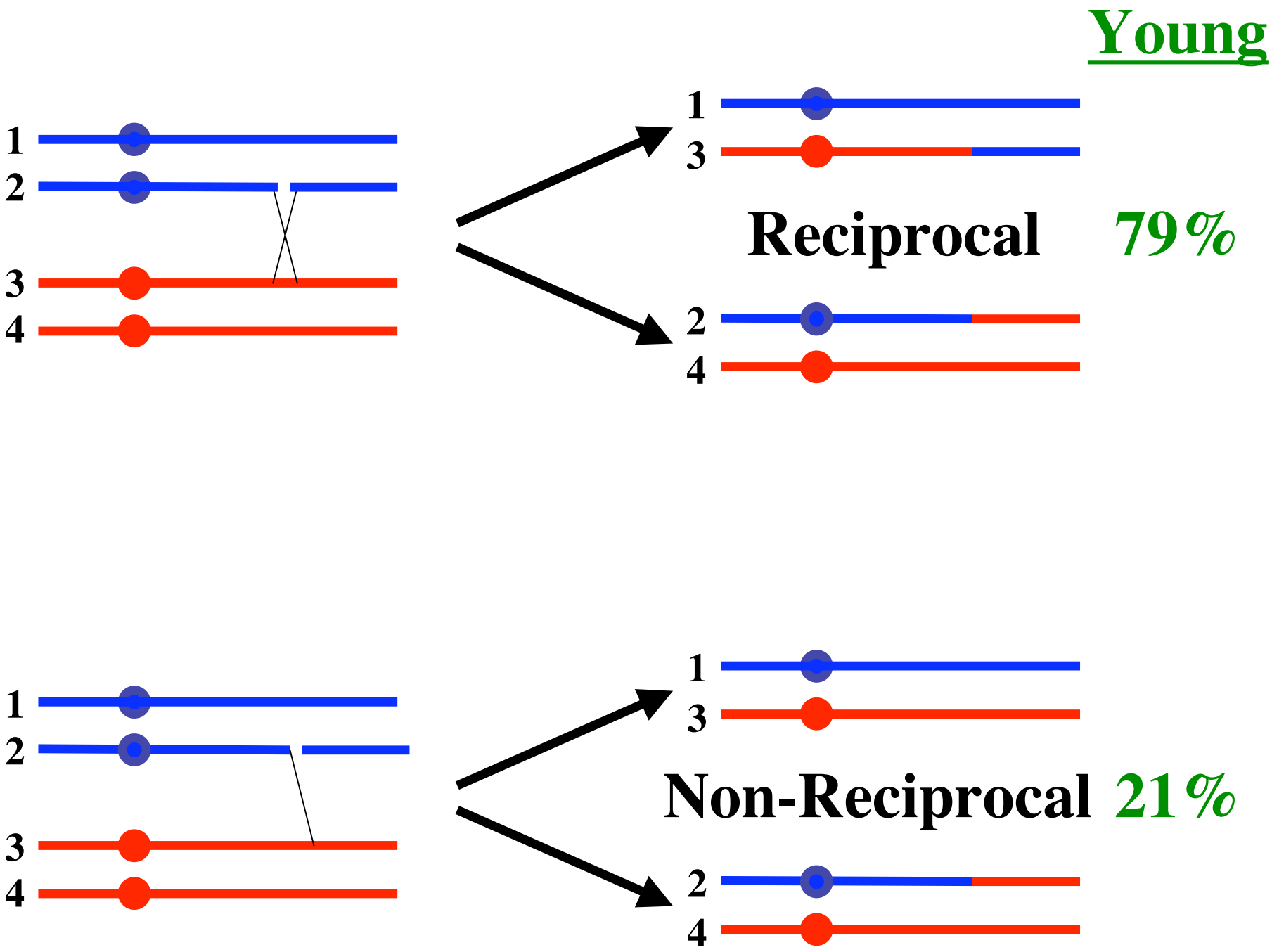
Recombination pathways for LOH

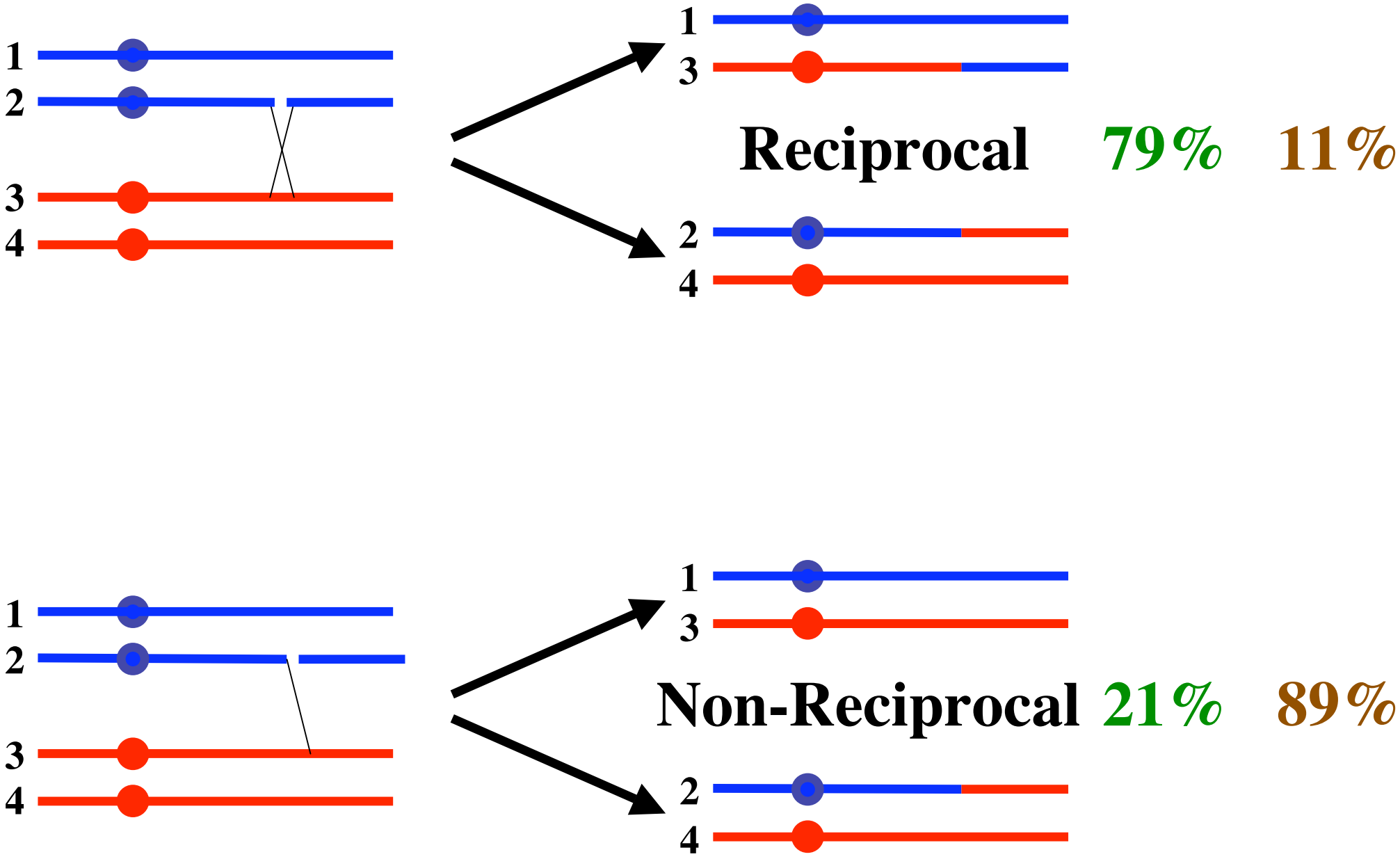


Recombination pathways for LOH

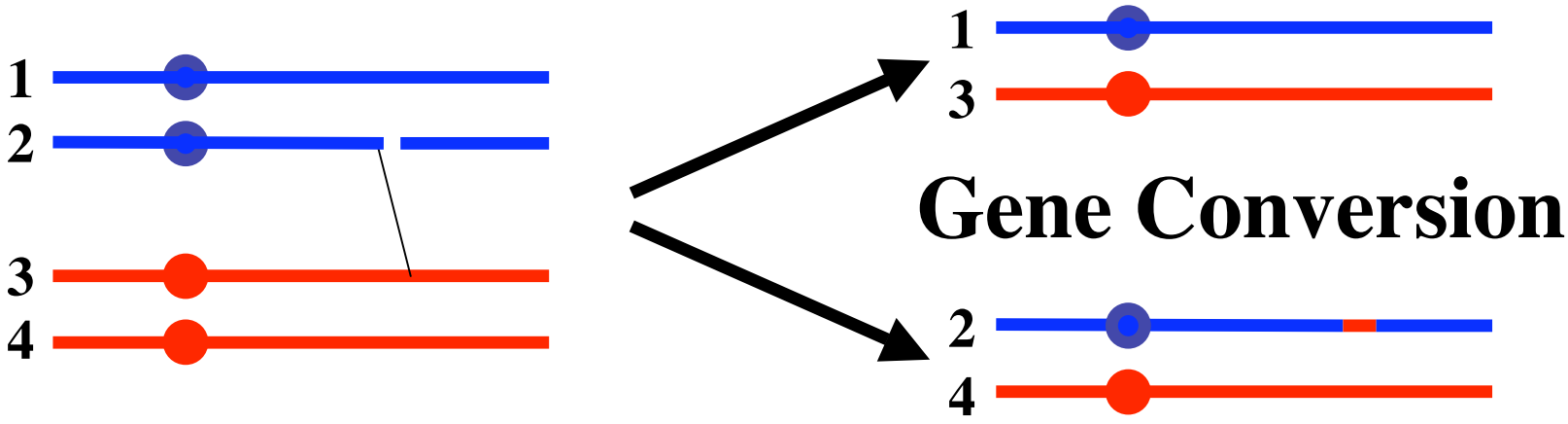


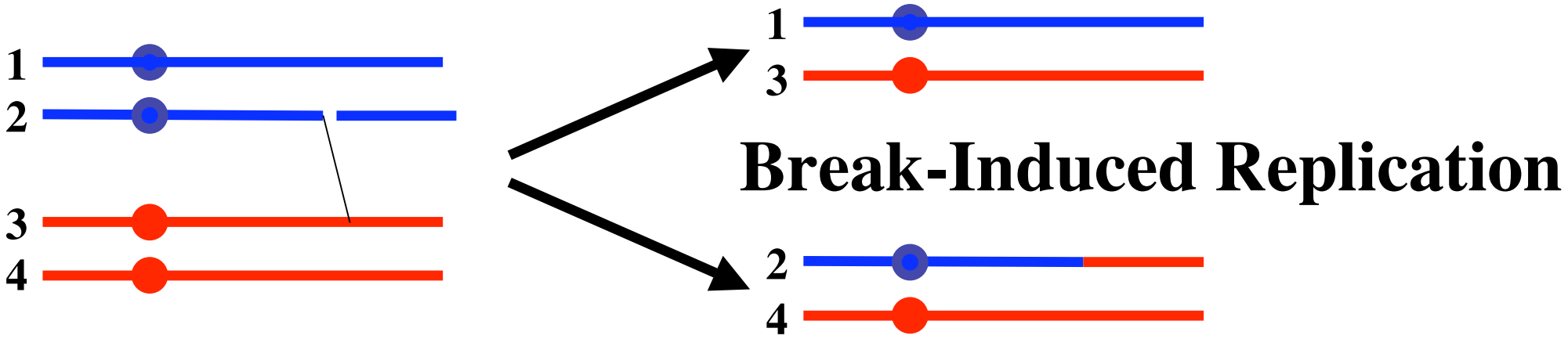



Young
1
2
3
4
1
3
Reciprocal
79%
2
4
1
2
3
4
1
3
Non-Reciprocal
21%
2
4

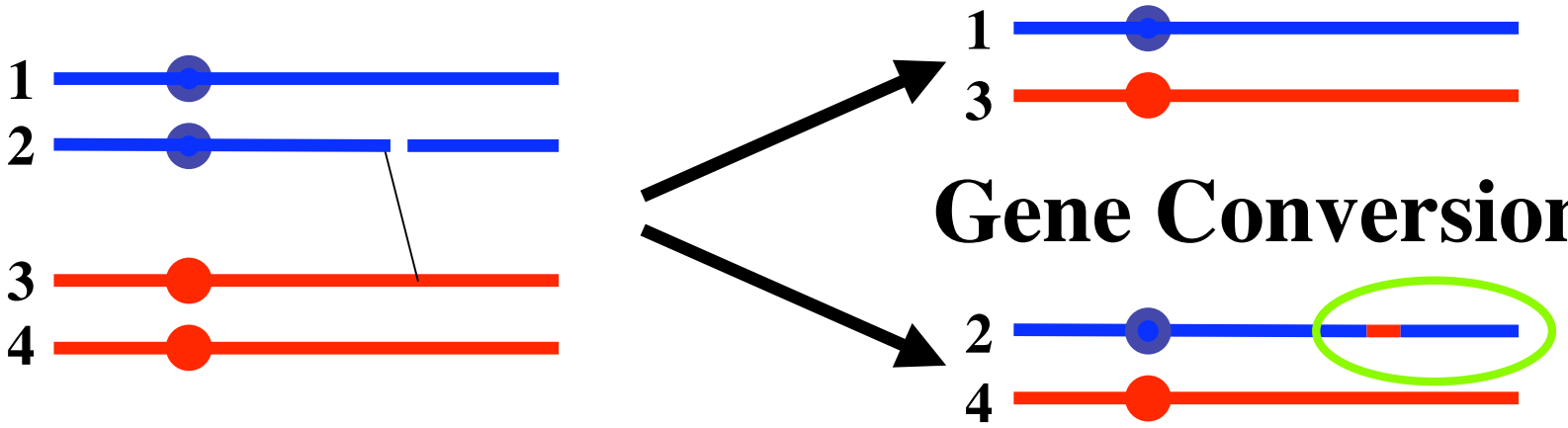

Young
Old
1
2
3
4
1
3
Reciprocal
79%
11%
2
4
1
2
3
4
1
3
Non-Reciprocal
21%
89%
2
4

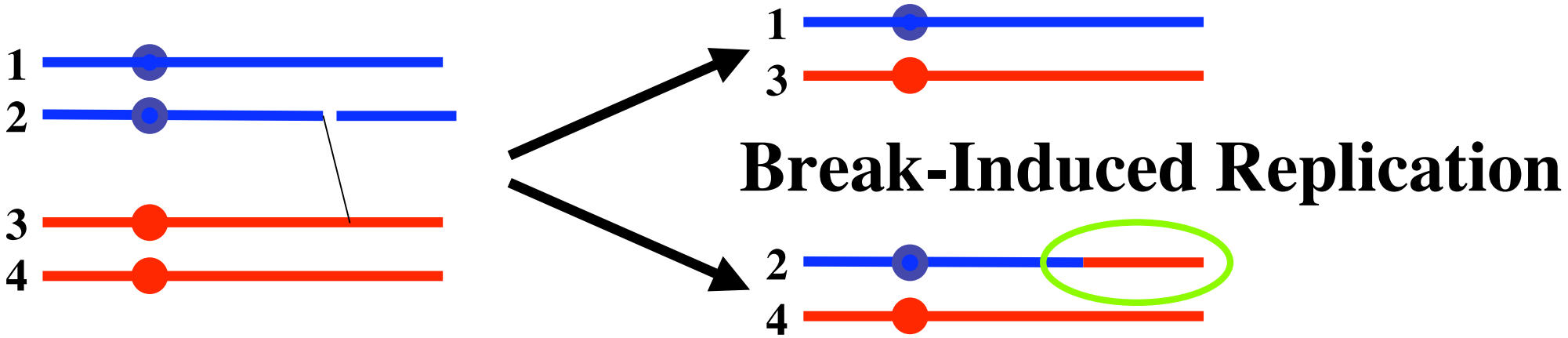
Non-reciprocal recombination pathways for LOH



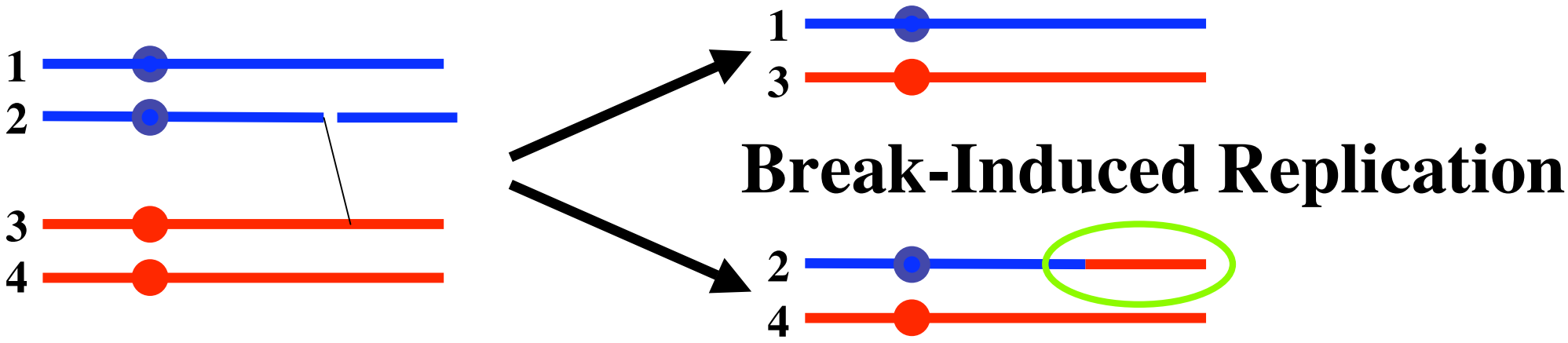


Non-reciprocal recombination pathways for LOH

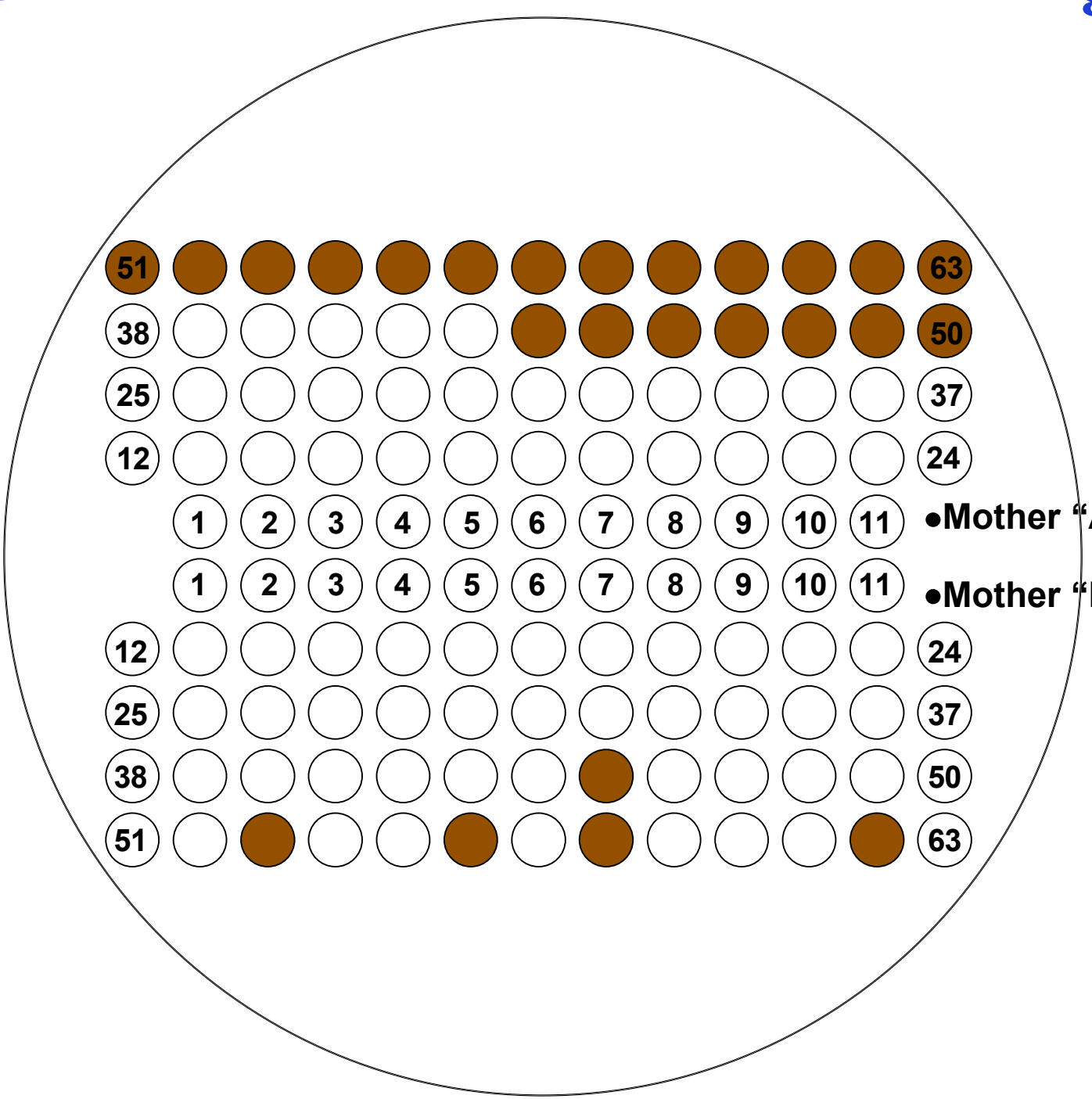




Age-induced LOH occurs by BIR



LOH events in mothers vs. daughters



LOH in mother

LOH in daughters

Asymmetry of LOH

MET15 LOH		*SAM2* LOH	
in mother	in daughter	in mother	in daughter
6	80	0	18

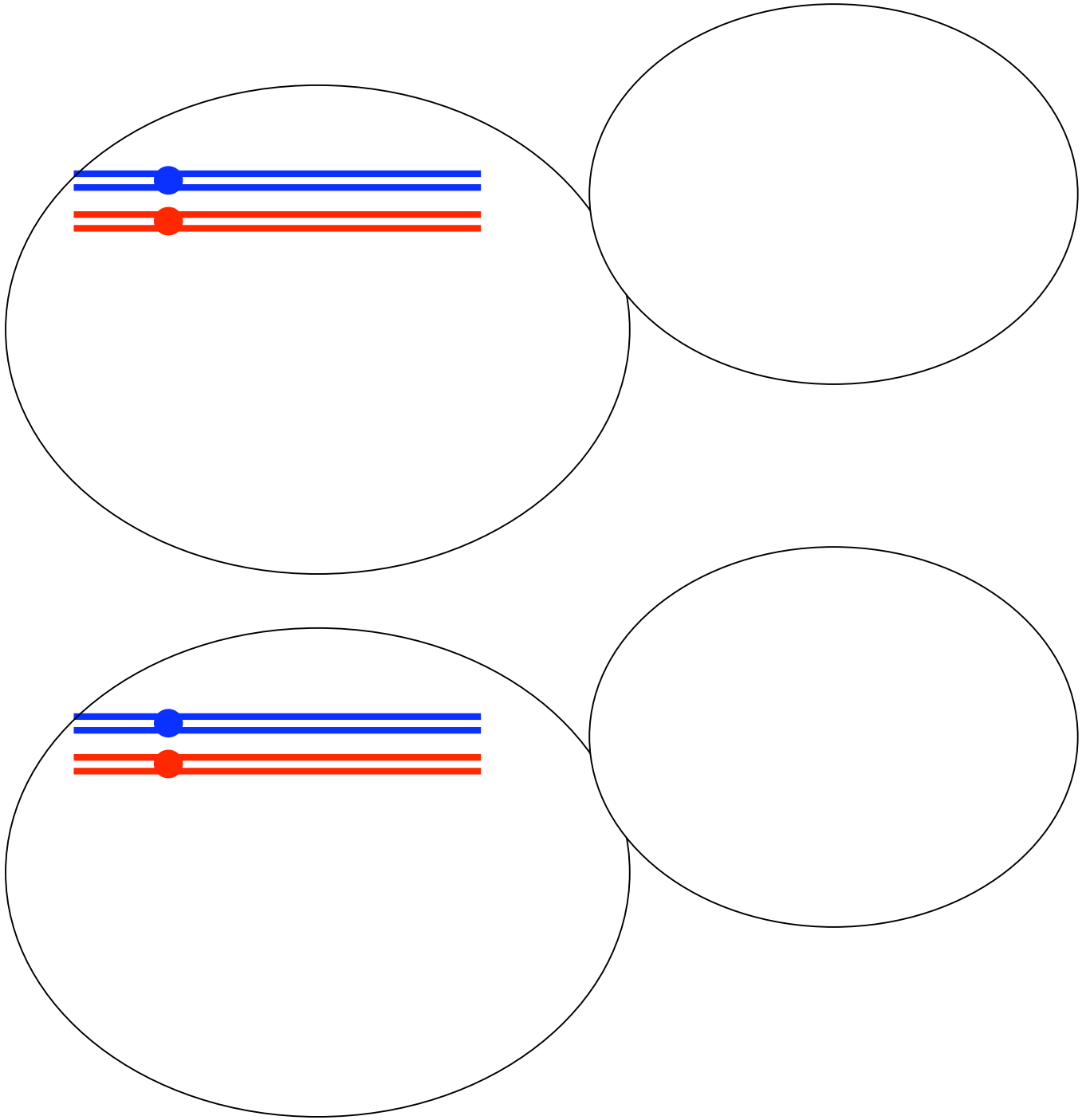
Asymmetry of LOH

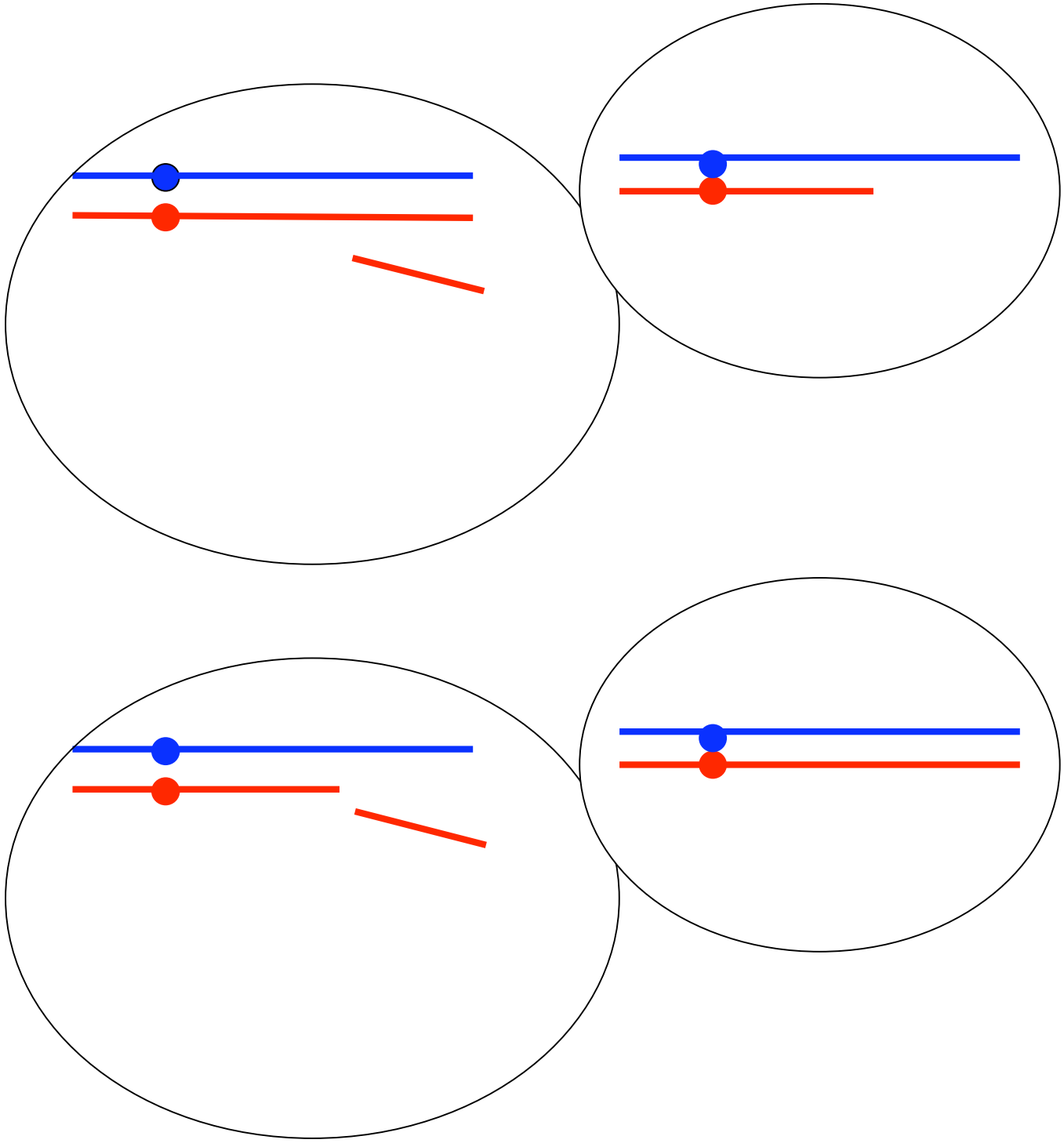
MET15 LOH		*SAM2* LOH	
in mother	in daughter	in mother	in daughter
6	80	0	18

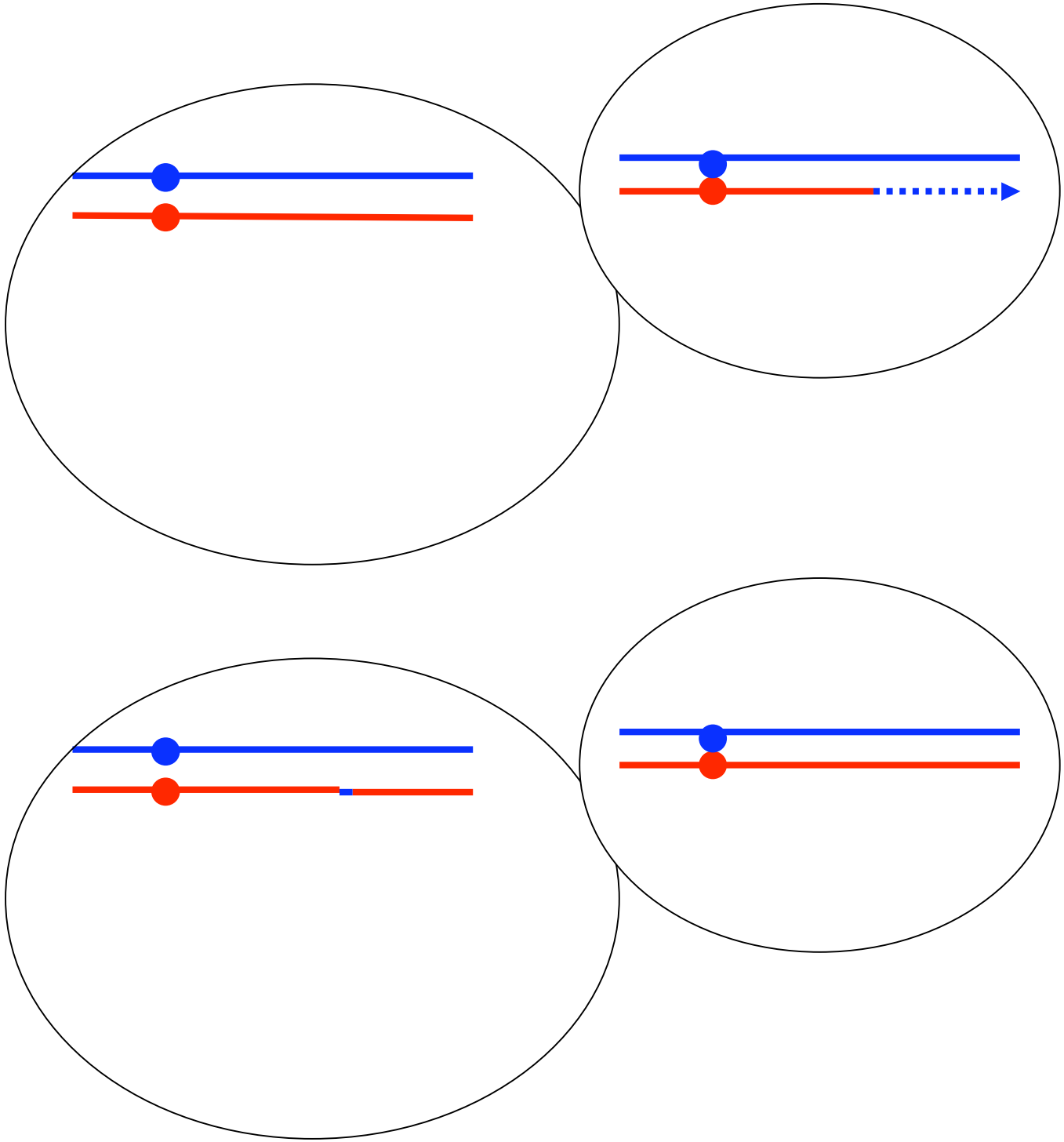
Mother cells are recalcitrant to LOH as they age!

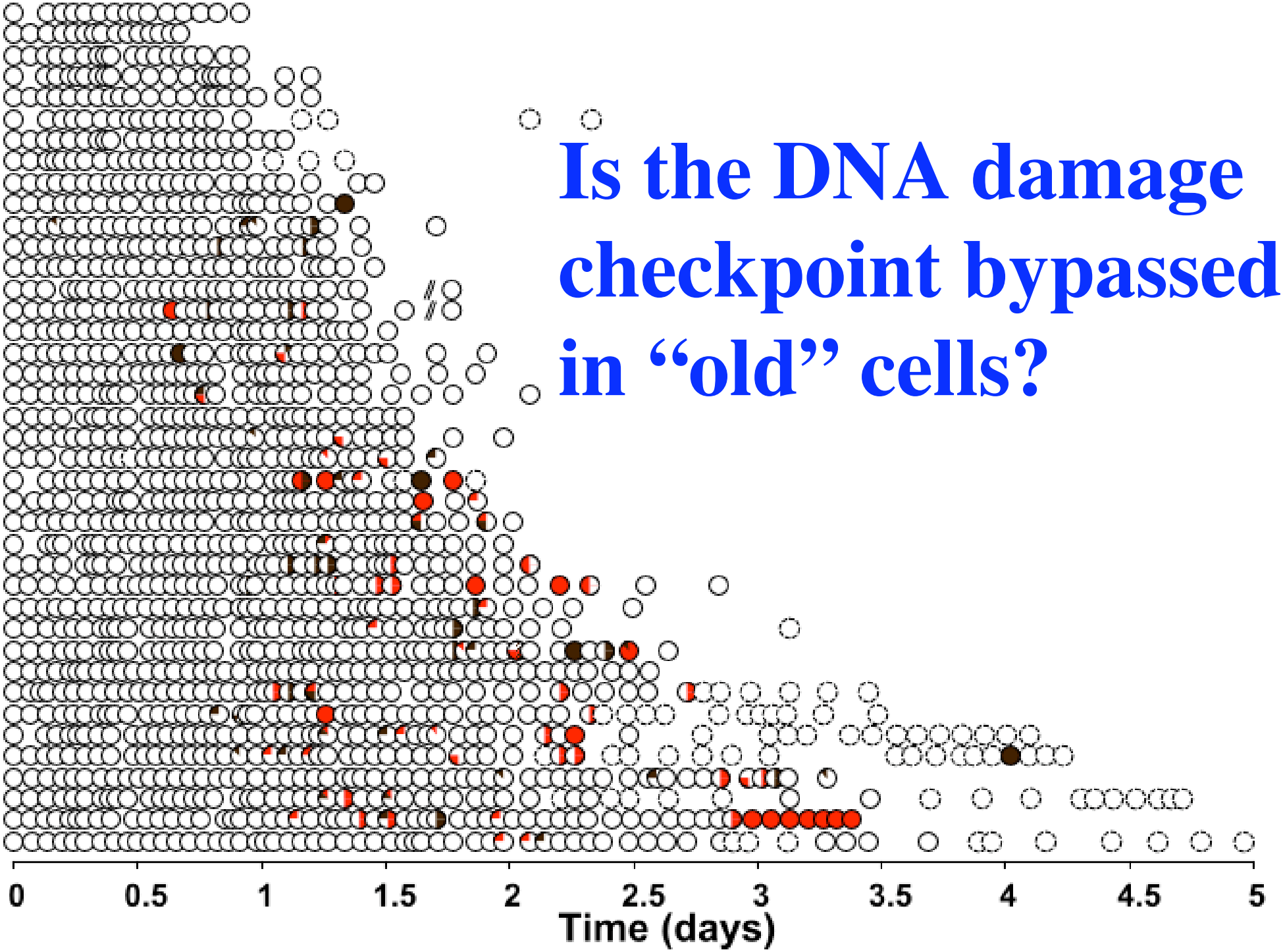
What is the basis for the asymmetry in age-induced LOH?

- **Mother cells "know" to keep the good chromosome.** **(A type of Cairns hypothesis *Nature*, 1975)**
- **Broken acentric chromosome fragments are preferentially retained in the mother.** **(Murray & Szostak, 1983.)**





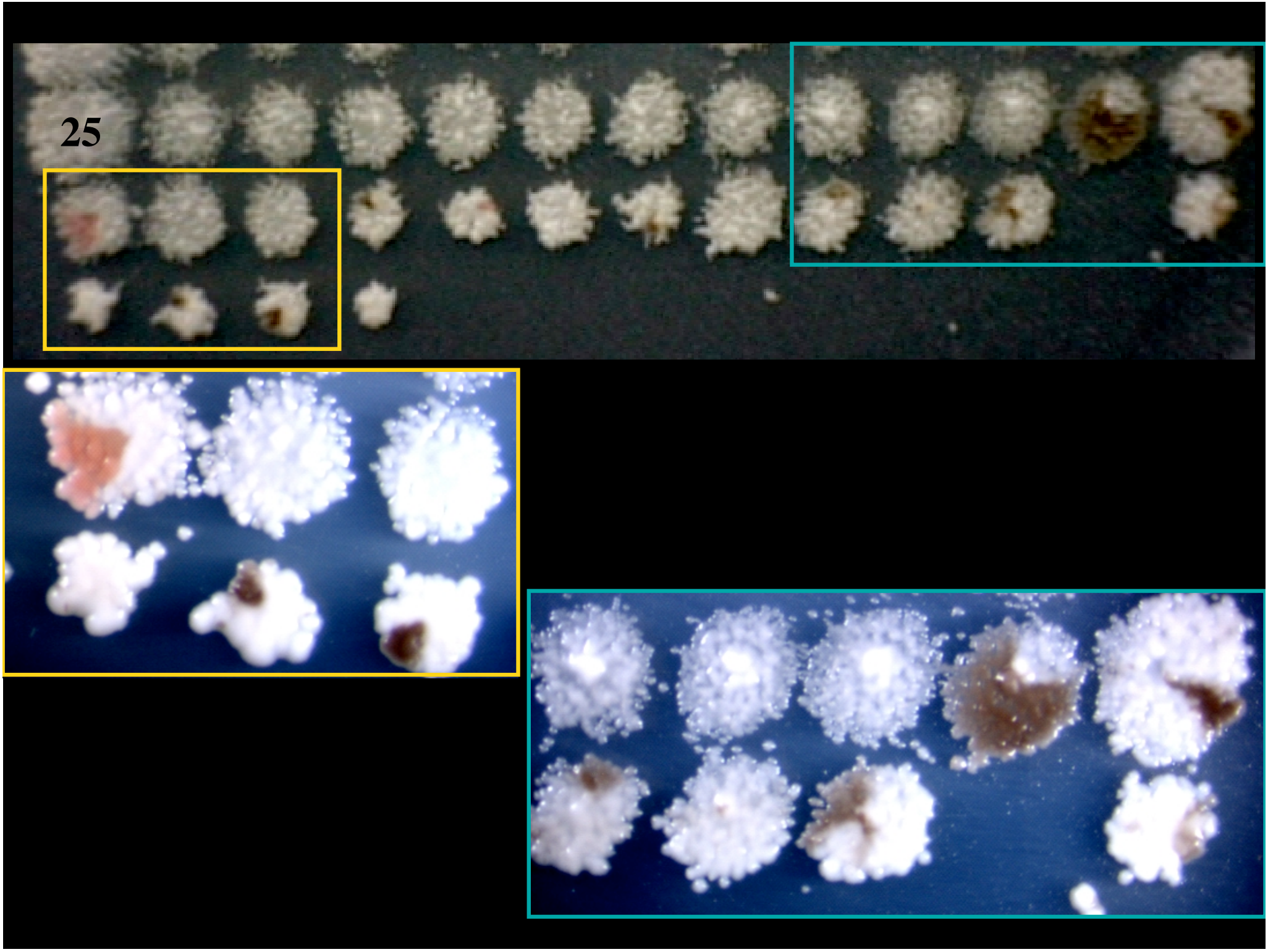



Is the DNA damage checkpoint bypassed in “old” cells?
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5
5
Time (days)

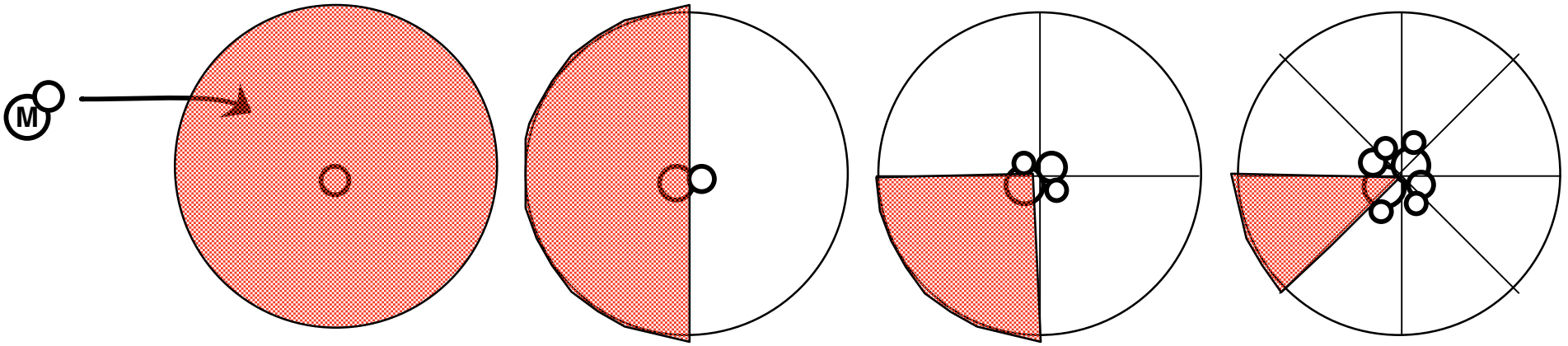
LOH in aging yeast cells

- **Age-dependent increase in LOH**
- **“Switch” to ~100x higher rate**
- **All recombination - linked to DNA damage - distinct from young cells**
- **Age-related increase in LOH is on its own “clock”**
- **Loss of DNA damage checkpoint?**

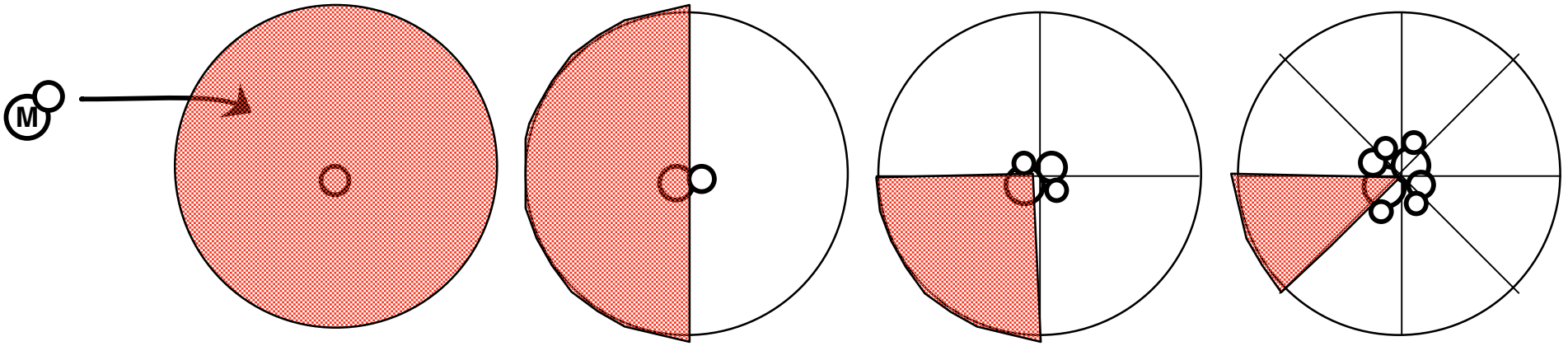
Is the Age-induced LOH switch permanent?


25

Resetting the Switch

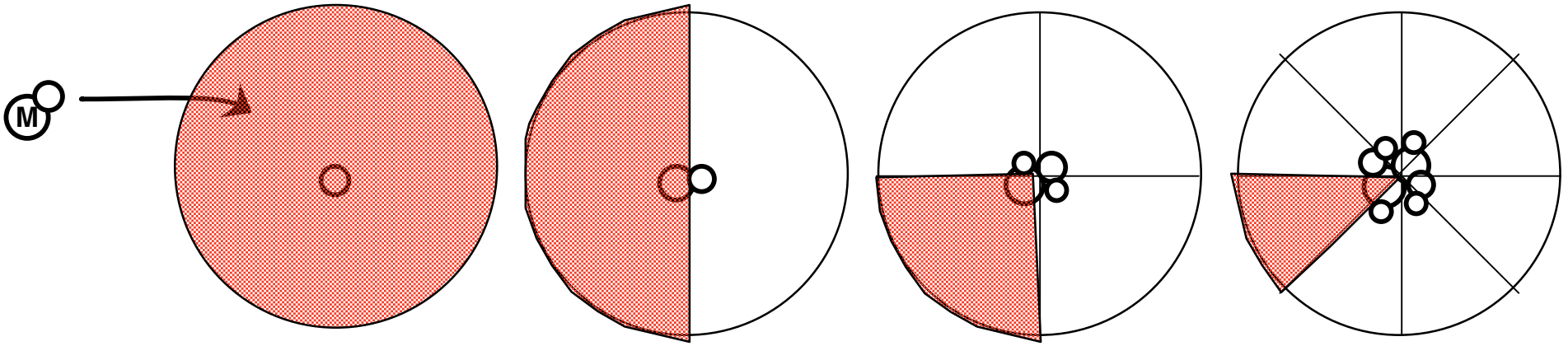


Resetting the Switch



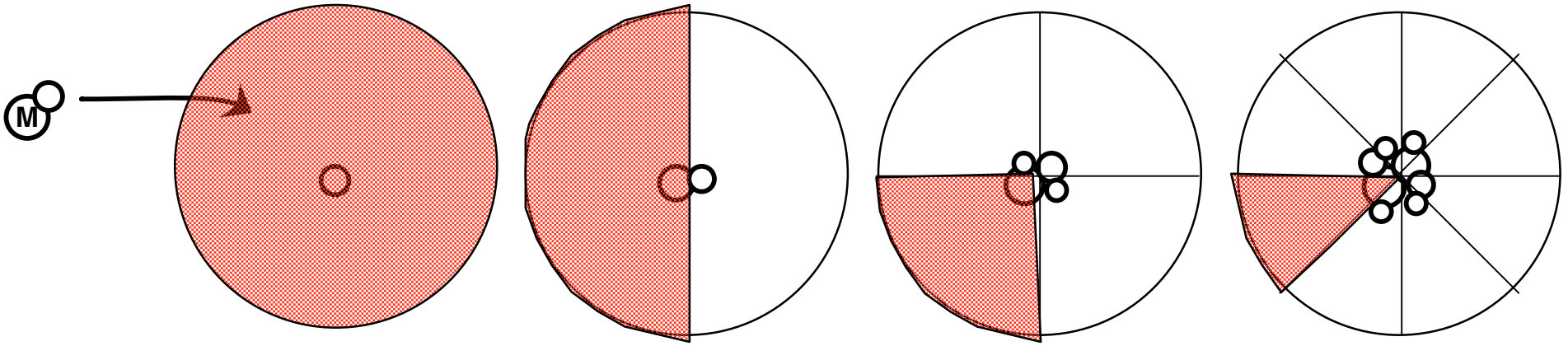
	Half-sectored	Quarter-sectored	Eighth-sectored
Expected	1X	2X	4X

Resetting the Switch



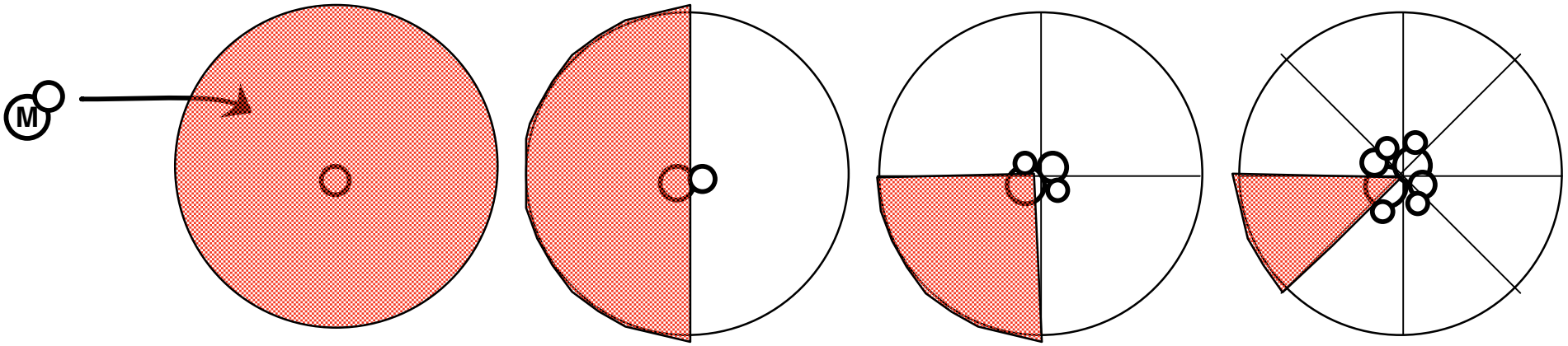
	Expected	Half-sectored 1X	Quarter-sectored 2X	Eighth-sectored 4X
Young cells		41 (0.9)	96 (2)	257 (5.3)

Resetting the Switch



Expected	Half-sectored 1X	Quarter-sectored 2X	Eighth-sectored 4X
Young cells	41 (0.9)	96 (2)	257 (5.3)
Old cells	74 (1)	102 (1.4)	81 (1.1)

Resetting the Switch



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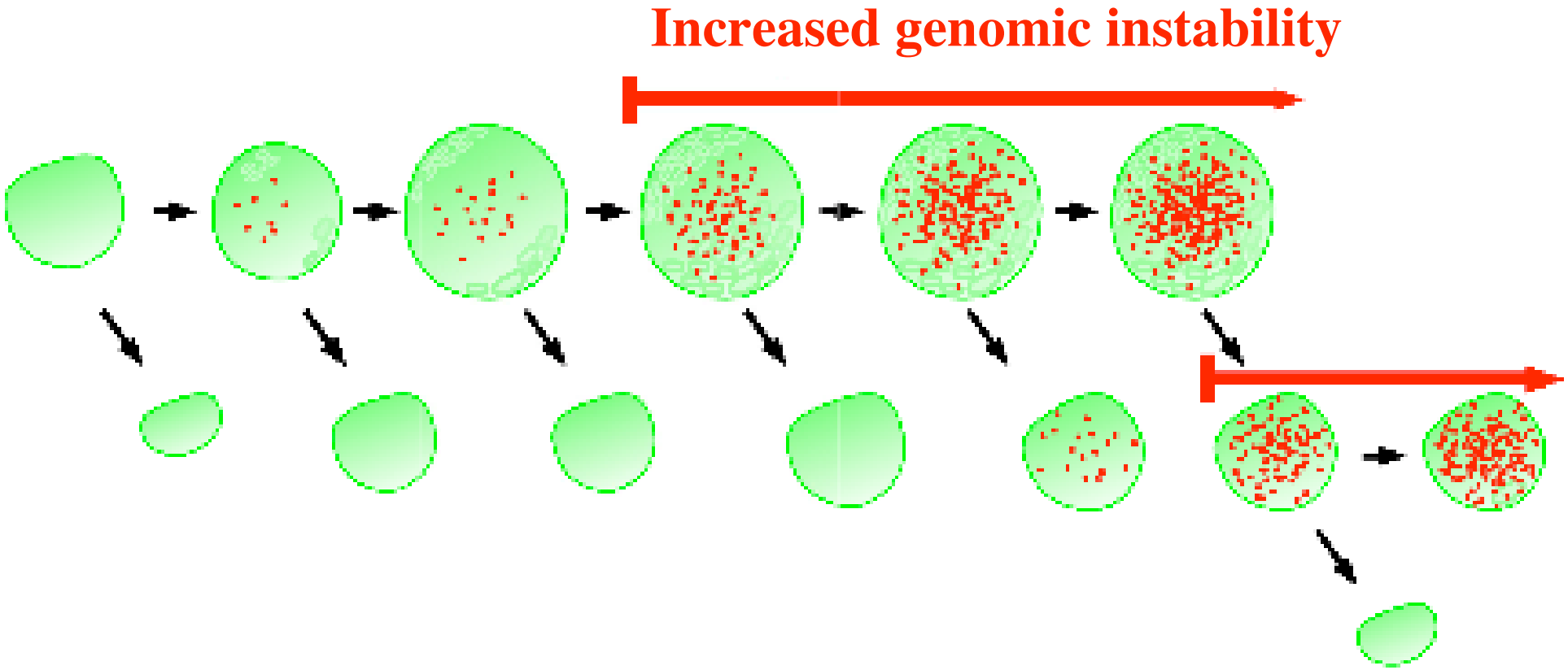
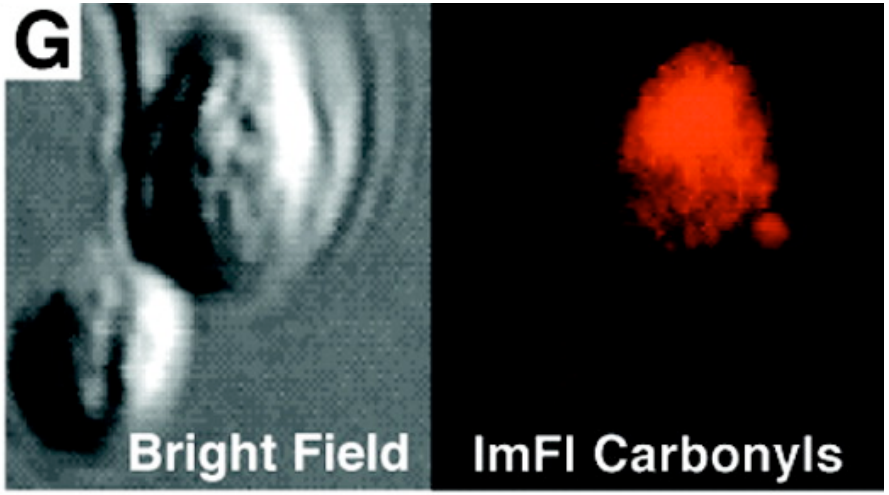
Expected	1X	2X	4X
Young cells	41 (0.9)	96 (2)	257 (5.3)
Old cells	74 (1)	102 (1.4)	81 (1.1)

The hyper-recombinational state is "diluted out" through progeny cells!

A genomic instability factor: buildup and dilution

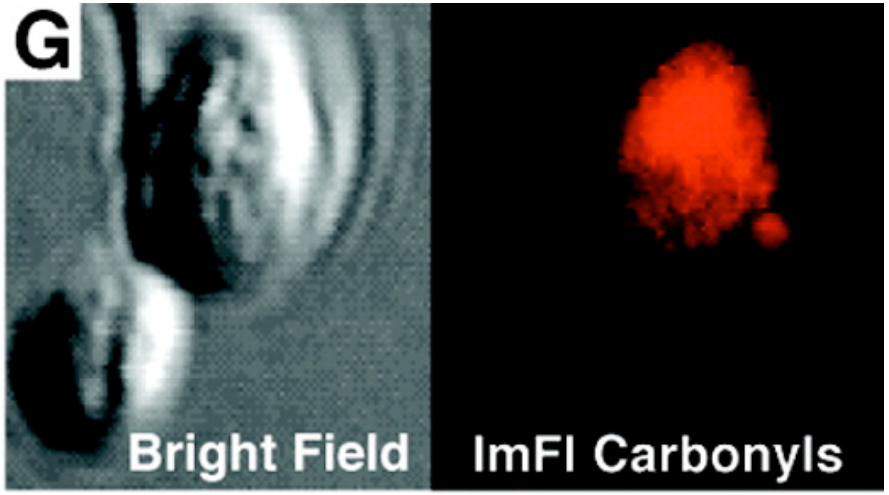


Could damaged protein cause age-induced LOH?



Aguilaniu, et al. *Science* 299:1751 (2003)

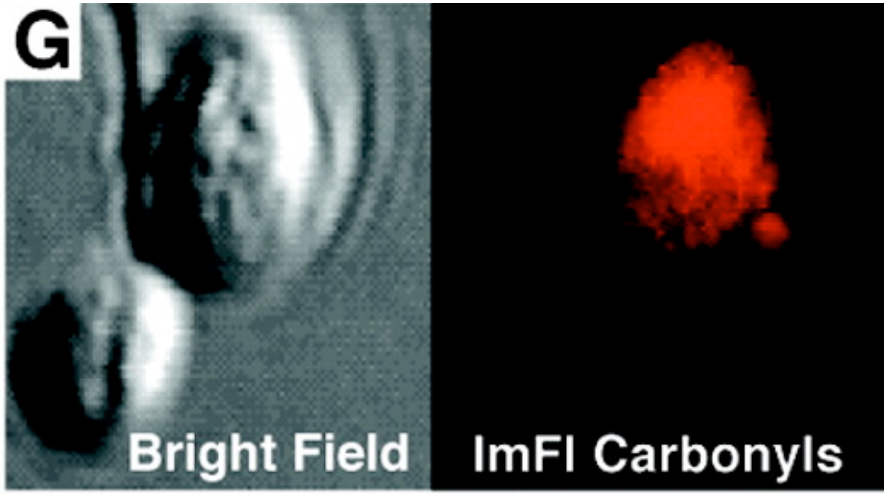
Could damaged protein cause age-induced LOH?



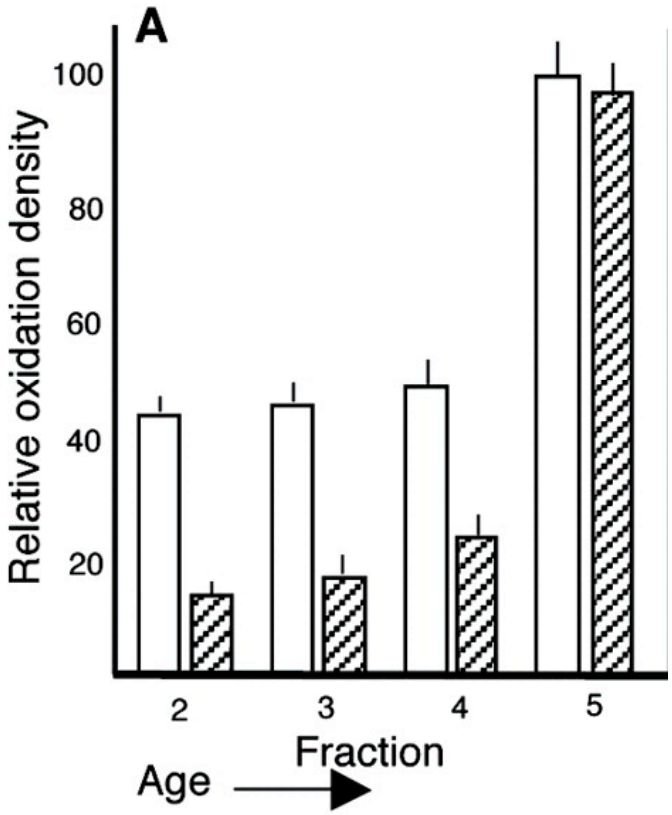
- **Damaged proteins accumulate in aging mother cells**

Aguilaniu, et al. *Science* 299:1751 (2003)

Could damaged protein cause age-induced LOH?



- Damaged proteins accumulate in aging mother cells



- Damaged protein is inherited by the progeny of older mothers

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