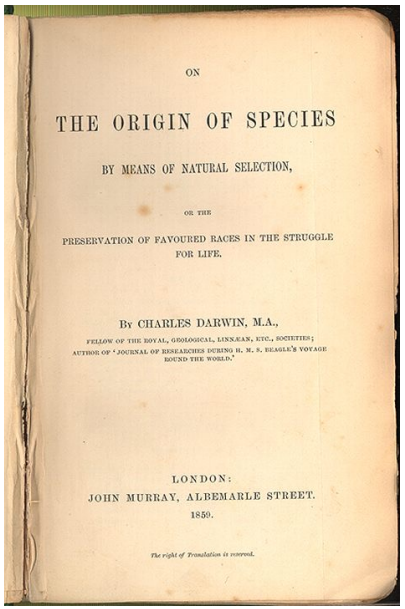
Darwin s'interrogeait :
pourquoi le pelage tortoise-shell se voit seulement chez des femelles ?

The nature of the bond of correlation is very frequently quite obscure. M. Is. Geoffroy St Hilaire has forcibly remarked, that certain malconformations very frequently, and that other rarely coexist, without our being able to assign any reason. **What can be more singular than the relation between** blue eyes and deafness in cats, and **the tortoise-shell colour with the female sex**;
p.183

Charles Darwin, vers 1849



ON

THE ORIGIN OF SPECIES

BY MEANS OF NATURAL SELECTION,

OR THE

PRESERVATION OF FAVOURED RACES IN THE STRUGGLE FOR LIFE.

By CHARLES DARWIN, M.A.,

FELLOW OF THE ROYAL, GEOLOGICAL, LINNEAN, ETC., SOCIETIES;
AUTHOR OF 'JOURNAL OF RESEARCHES DURING H. M. S. BEAGLE'S VOYAGE ROUND THE WORLD.'

LONDON:
JOHN MURRAY, ALBEMARLE STREET.
1859.

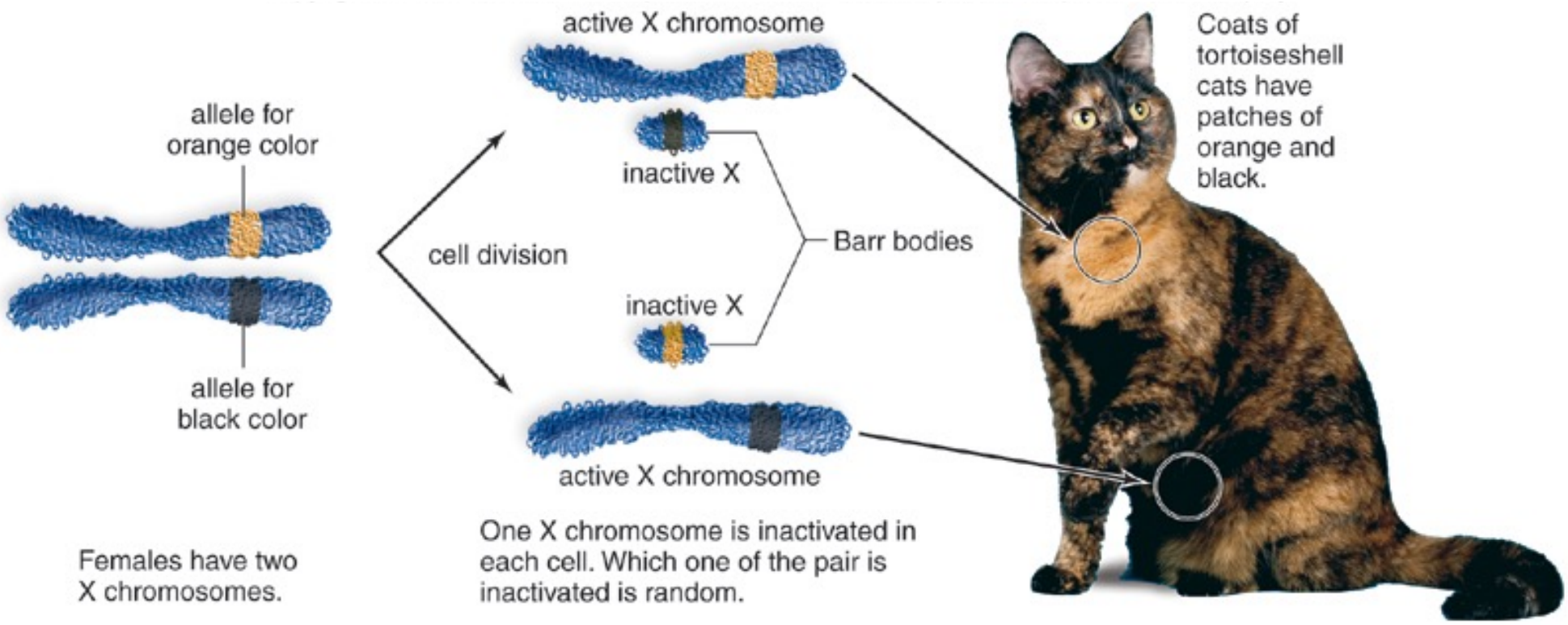
The right of Translation is reserved.

Inactivation of X chromosome

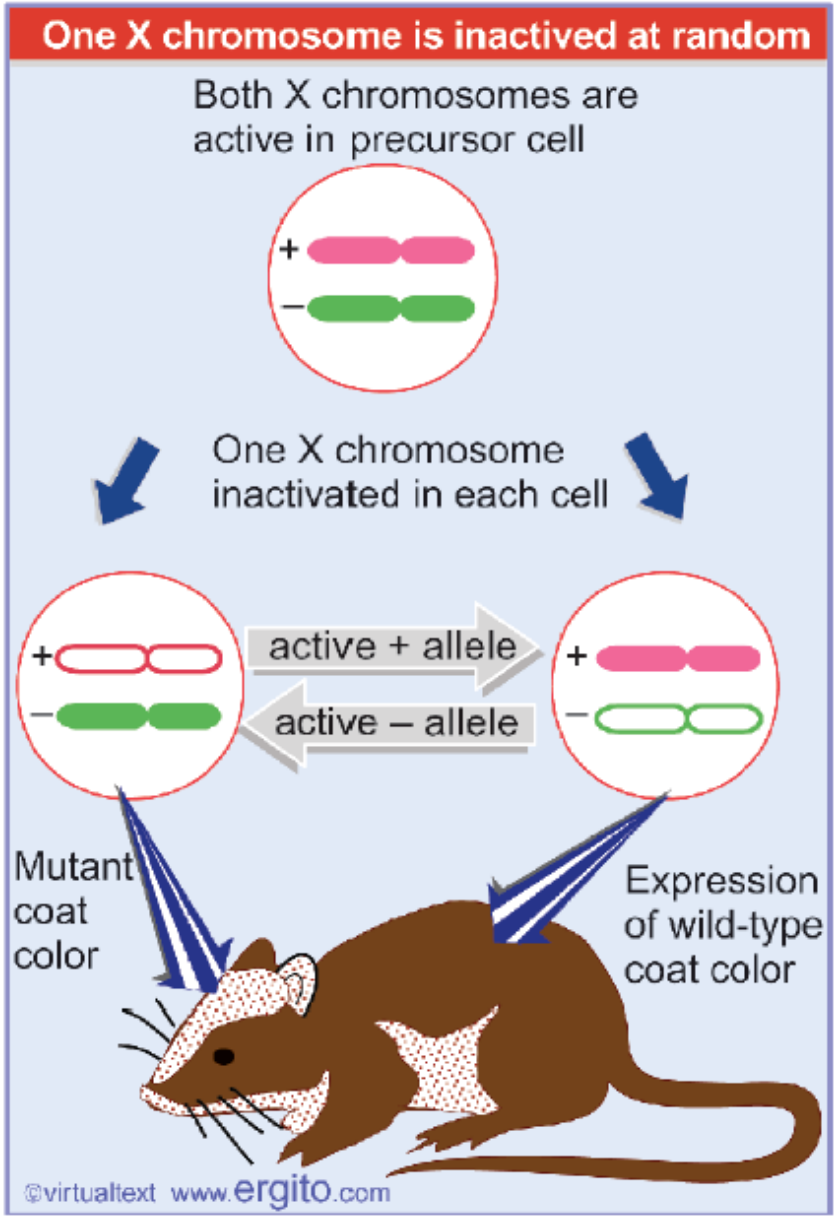
tortoiseshell
(≠ calico)

Figure 4-17
Genetics: A Conceptual Approach, Third Edition

X-inactivation



The inactive X chromosome is compacted and methylated

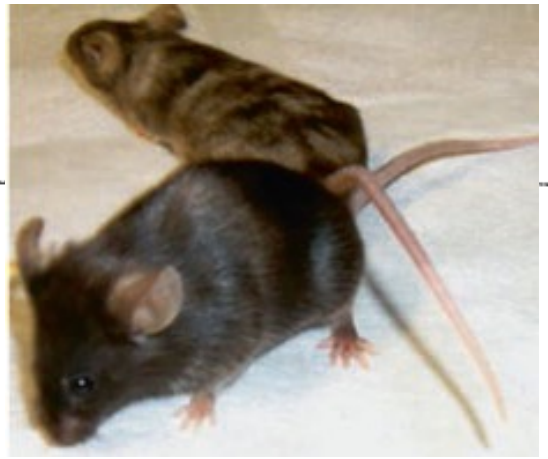

One X chromosome is inactived at random
Both X chromosomes are active in precursor cell
+
–
One X chromosome inactivated in each cell
+
–
active + allele
active – allele
+
–
Mutant coat color
Expression of wild-type coat color
©virtualtext www.ergito.com

Inactivation d’un chromosome X chez une souris femelle :

Régions foncées : X normal
Régions claires : X muté

TABLE 1. SEX-LINKED GENES IN THE MOUSE

Color	Skin	Other
Mottled	Tabby	Bent-tail
Brindled	Scurfy	Jimpy
Tortoiseshell		Gyro
Dappled		
Dappled-2		
26K		
4 translocations involving:		
Brown		
Albino alleles		
Pink-eye		



Mary LYON

Lyon, M. F. 1962.
Sex chromatin and gene action in the mammalian X-chromosome.
Am. J. Hum. Genet. 14:135-48

as those in the mouse. The coat of the tortoiseshell cat, being a mosaic of the black and yellow colours of the two homozygous types, fulfils this expectation.

MARY F. LYON

Medical Research Council
Radiobiological Research Unit,
Harwell, Didcot.

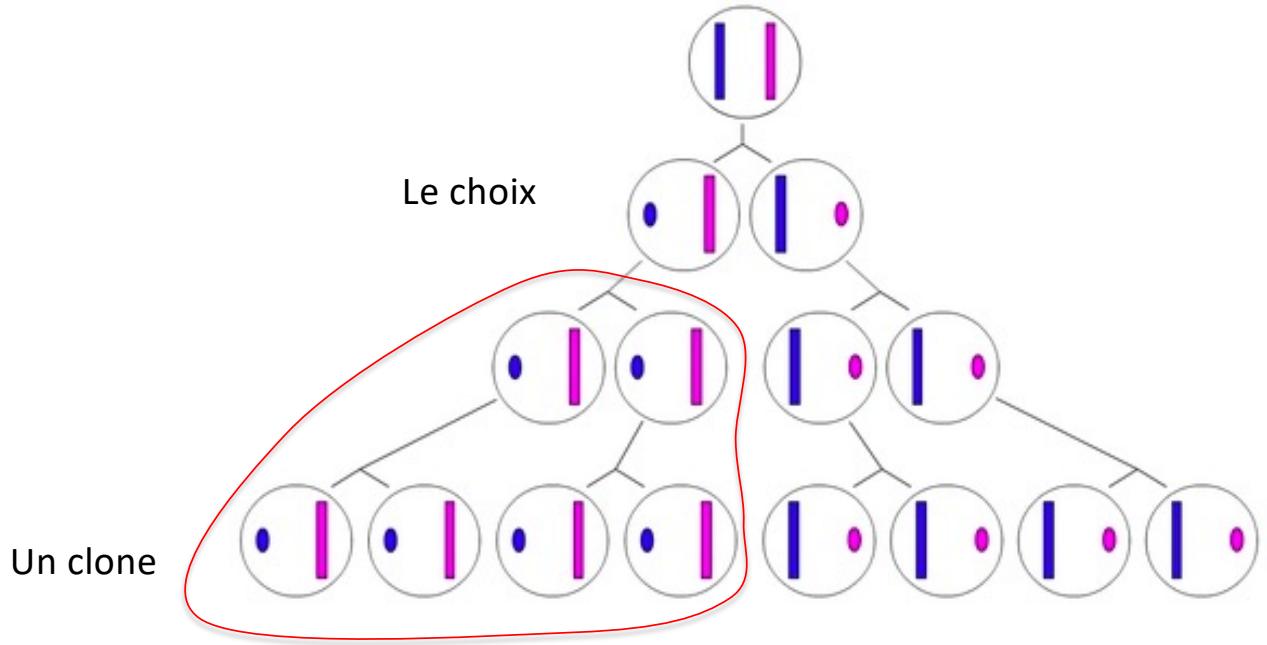
L'article dans Nature se termine par l'indication que l'hypothèse de l'inactivation d'un X explique la fourrure des chatte tortoiseshell.

Trois points essentiels à connaître sur l'inactivation du X.

① L'inactivation se produit vers le 20ème jour du développement embryonnaire. Les femmes reçoivent un chromosome X de leur mère **XM** et un chromosome X de leur père **XP**. Pendant une vingtaine de jours, les deux chromosomes X sont actifs. Par la suite un seul chromosome X est actif.

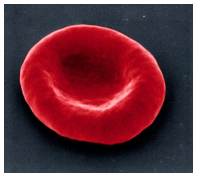
② Le choix du chromosome inactivé est *aléatoire*.

③ Le choix effectué par une cellule vers le 20ème jour est maintenu dans toutes les cellules descendant de cette cellule.

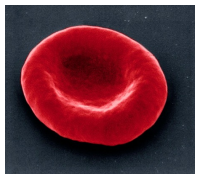


For genes located on the X chromosome
women (X X) should produce twice as much of a protein compare to men (only 1 X)

.

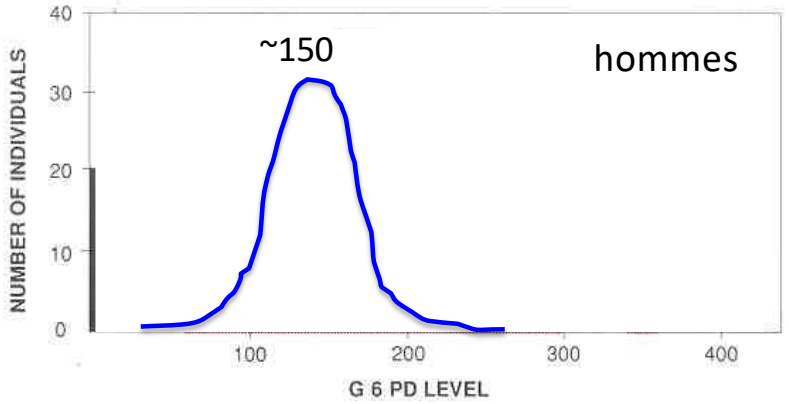


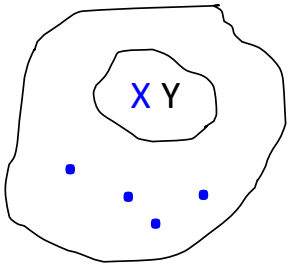
R. B. C.
from a man

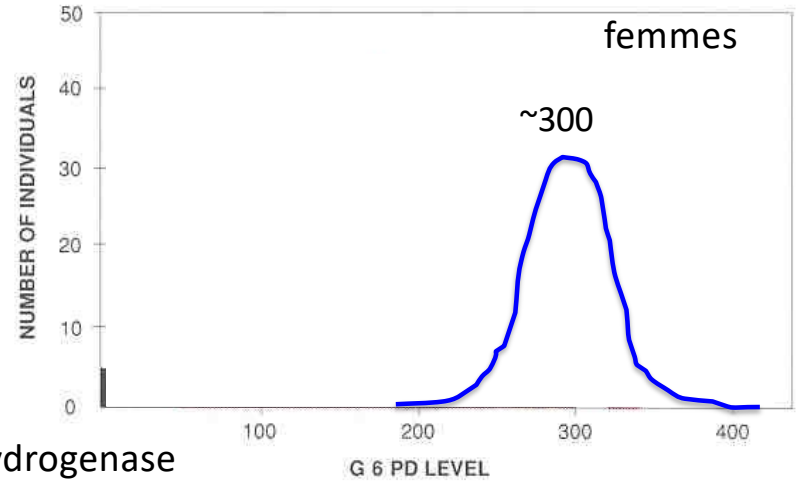


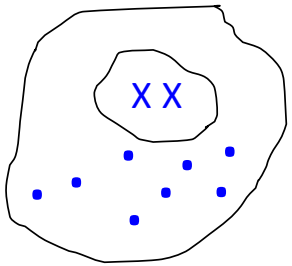
R. B. C. from
a woman

Theoretical expectation





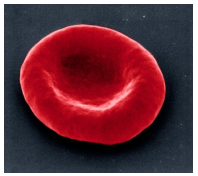




Glucose-6-Phosphate Dehydrogenase

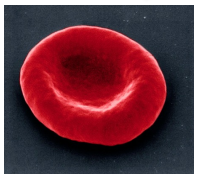
Observations do not confirm the expectation.

G6PD gene is located on X chromosome.



R. B. C. from a man

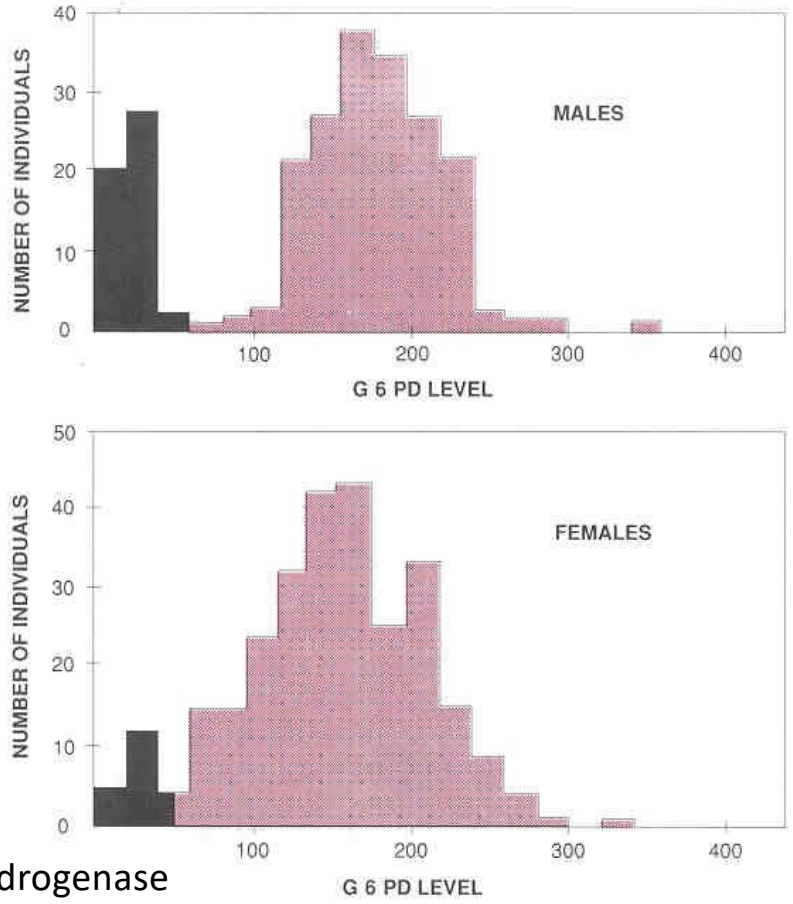
Identical amount of G6PD



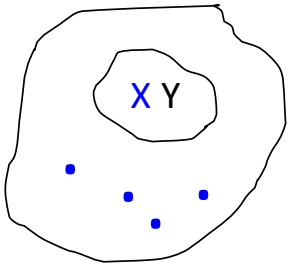
R. B. C. from a woman

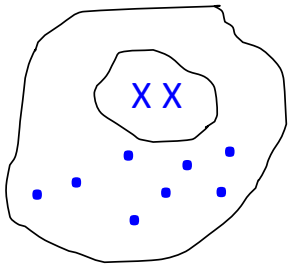
Glucose-6-Phosphate Dehydrogenase

Observation :



Theoretical expectation:

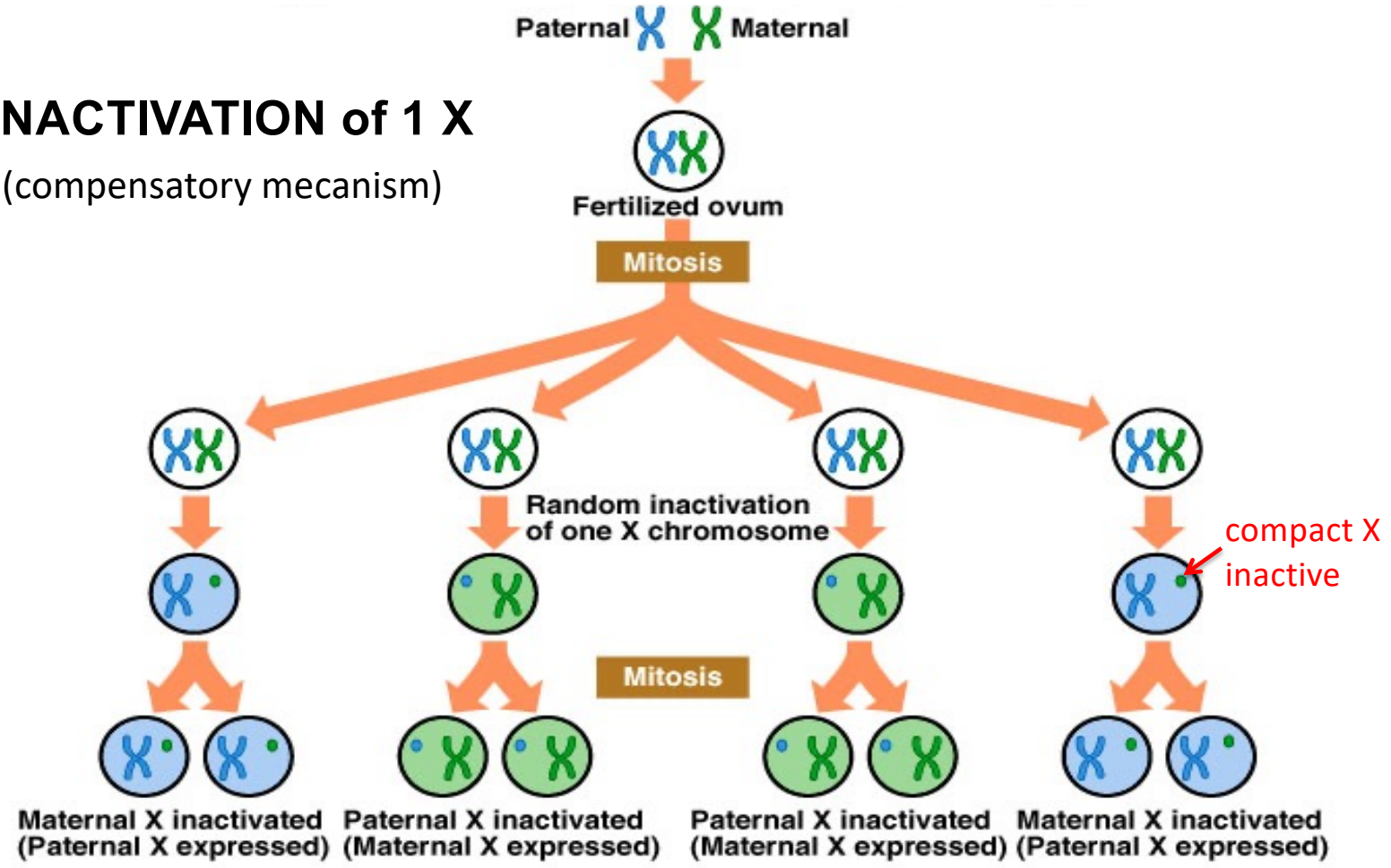




Women and men have the same amount of G6PD
because women and men have only 1 **active** X chromosome.

INACTIVATION of 1 X

(compensatory mecanism)



Difference between calico and tortoiseshell

(a)

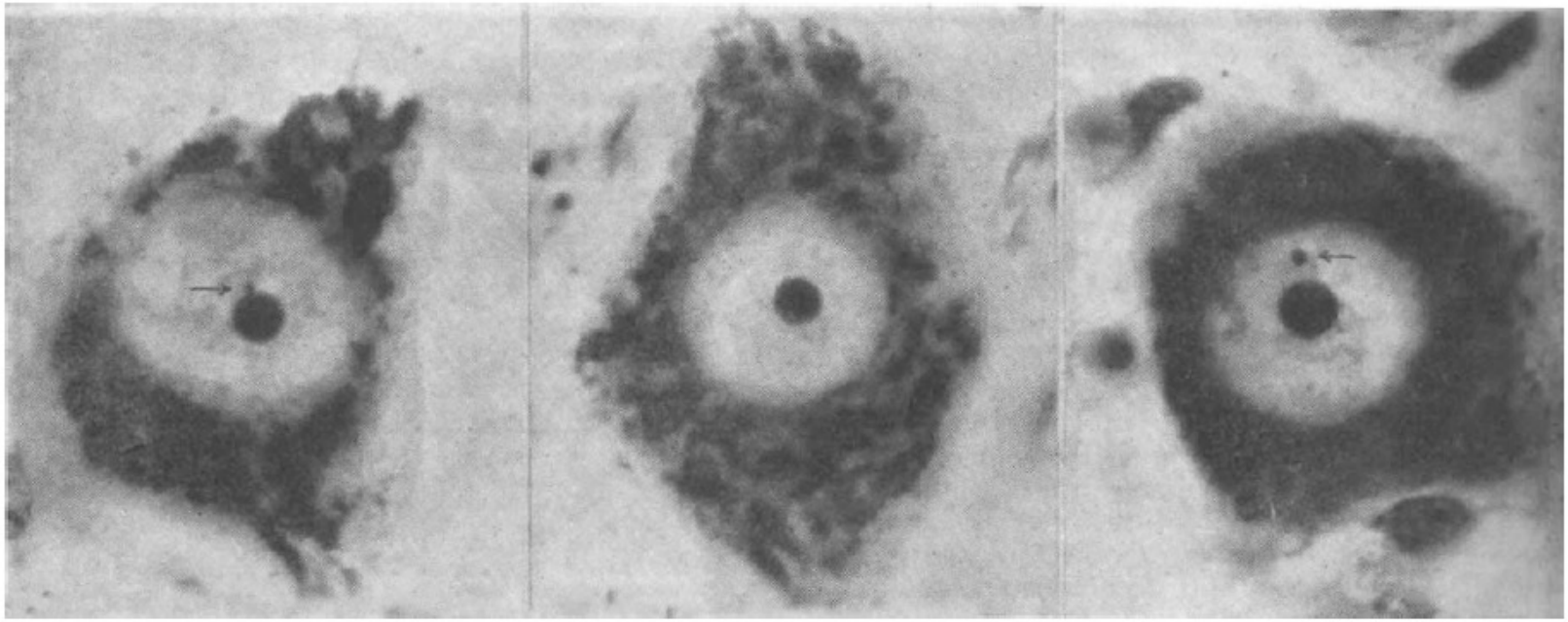
There is no melanocyte

(b)

Ewart BERTRAM

A Morphological Distinction between Neurones of the Male and Female, and the Behaviour of the Nucleolar Satellite during Accelerated Nucleoprotein Synthesis

Murray BARR
(1908-1995)

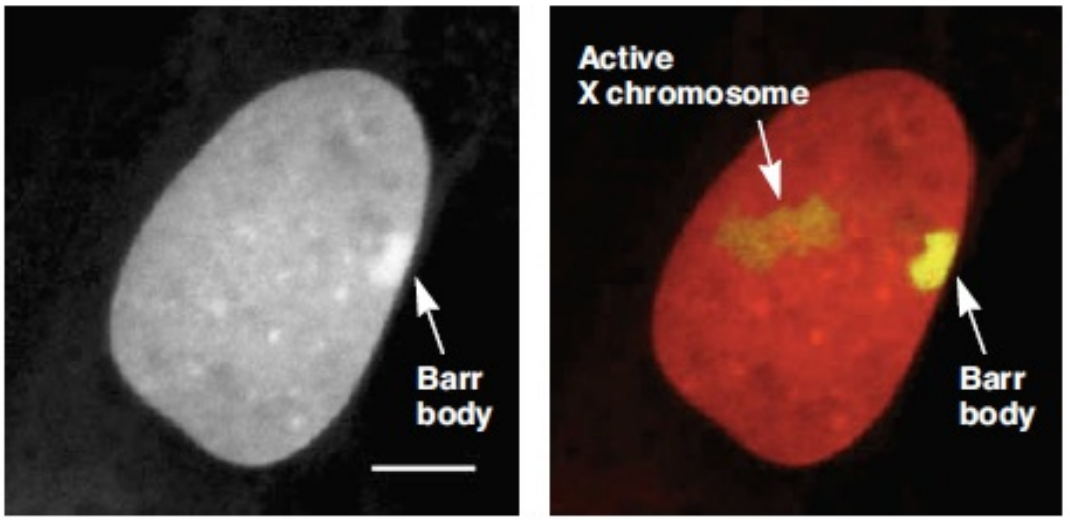


XX Fig. 1

XY Fig. 2

Fig. 3 XX

In 1949, Murray Barr and Ewart Bertram identified a highly condensed structure in the interphase nuclei of somatic cells in female cats that was not found in male cats.
This structure became known as the **Barr body**.



(a) Nucleus with a Barr body

In 1960, Susumu Ohno correctly proposed that the Barr body is a highly condensed X chromosome.

Barr body

(inactivated X chromosome)

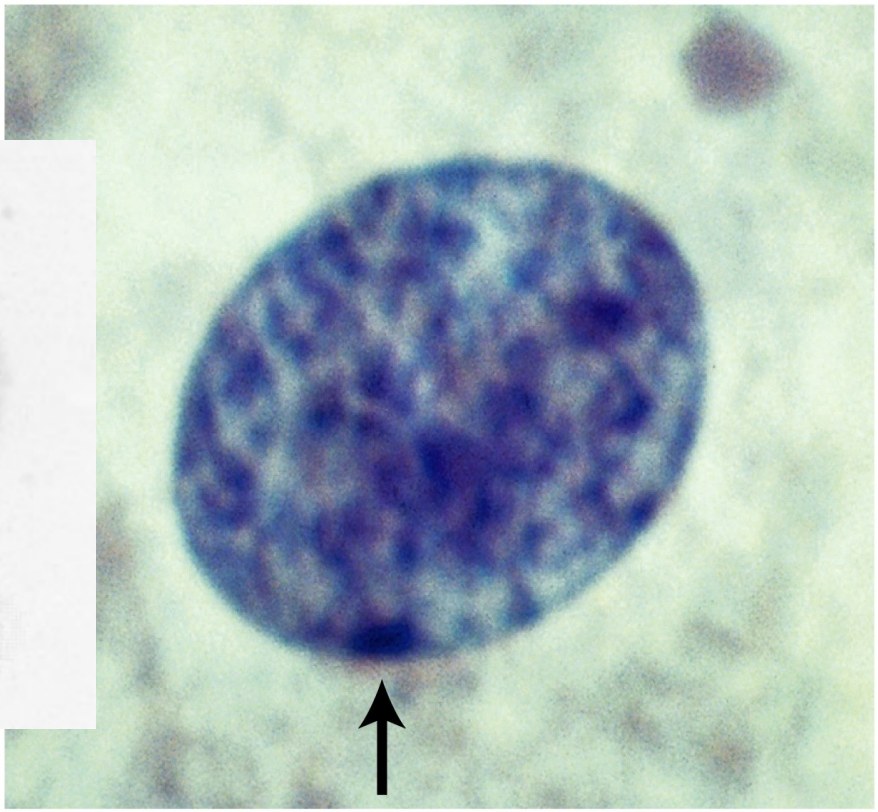
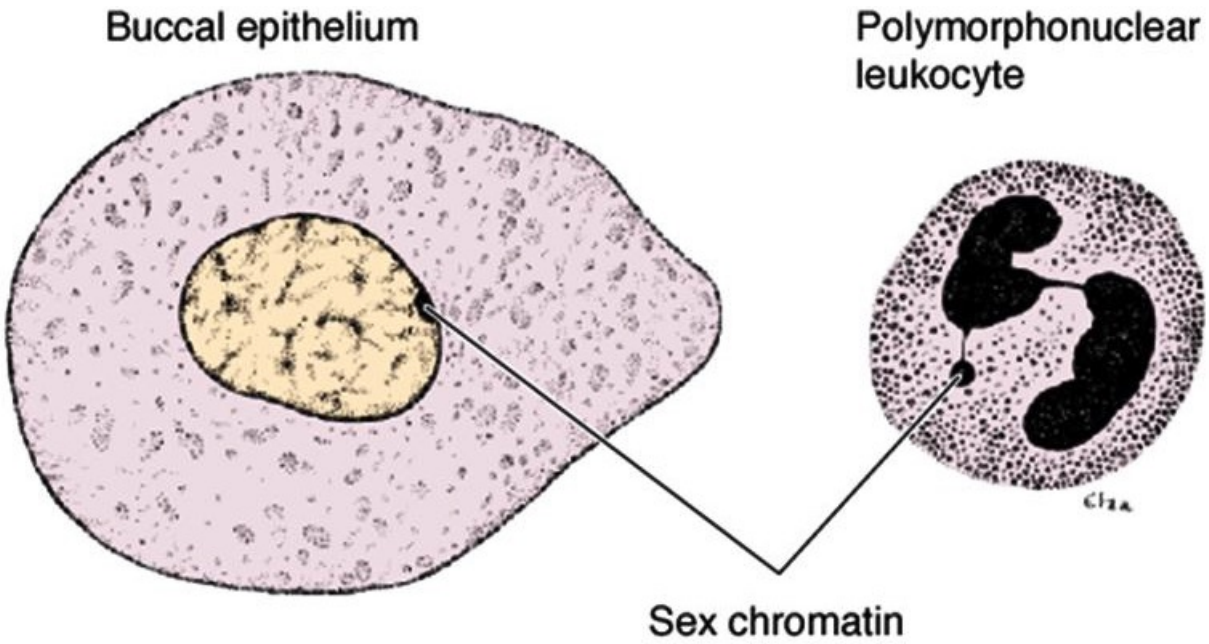


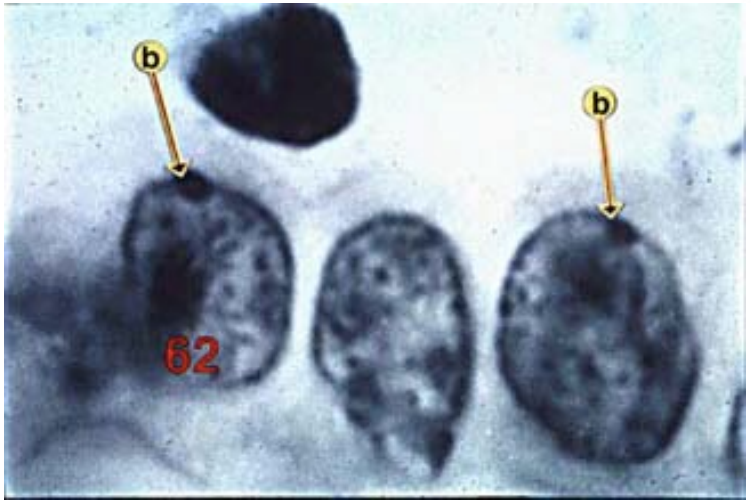
Figure 4-16a
Genetics: A Conceptual Approach, Third Edition

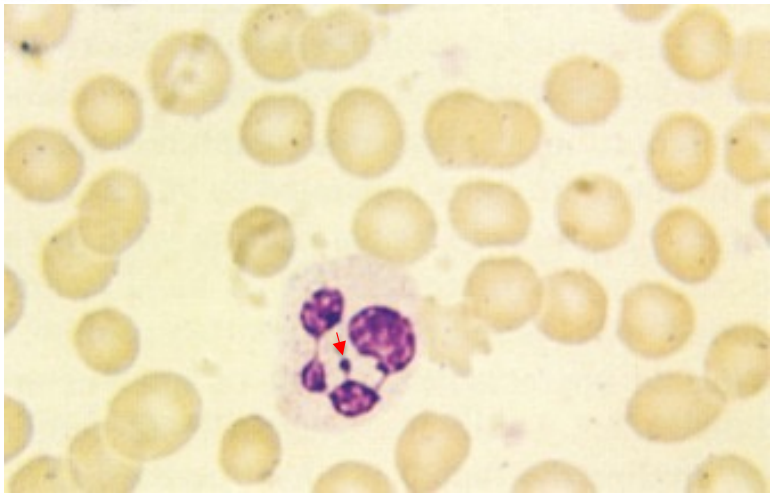
Barr body



Blood sample

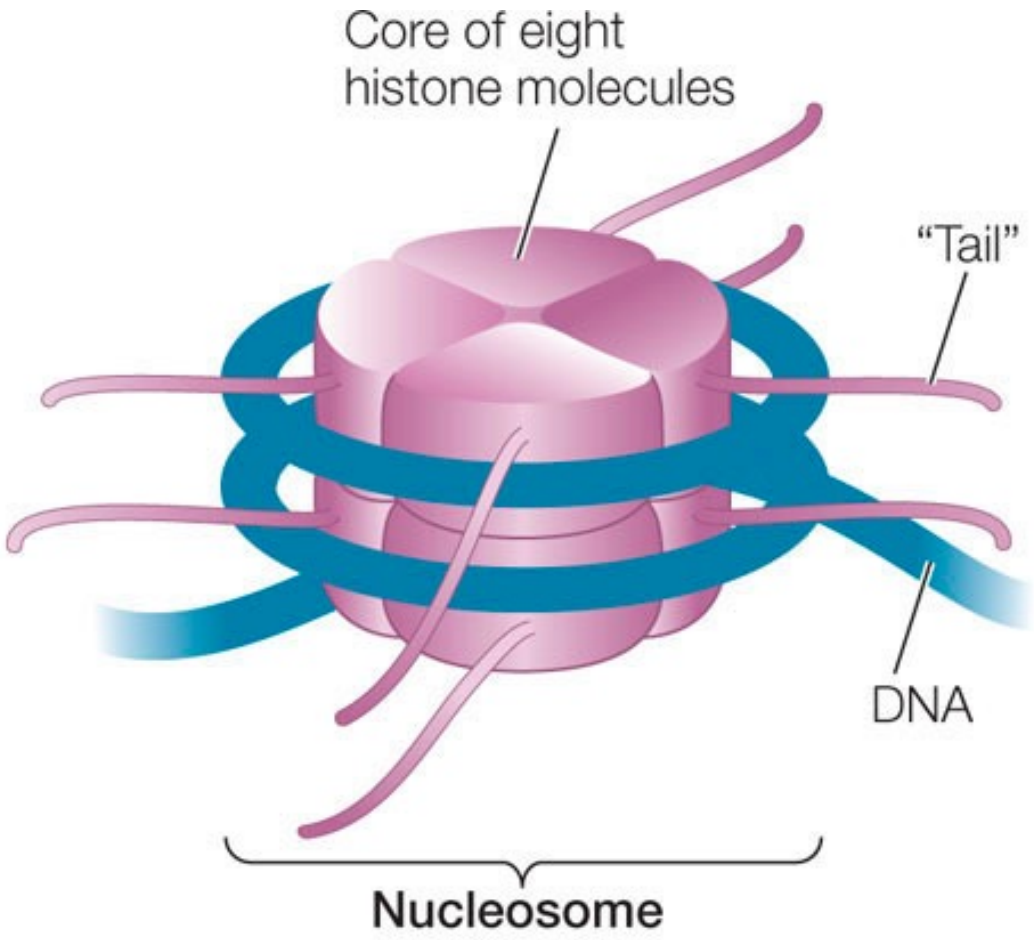
drumstick



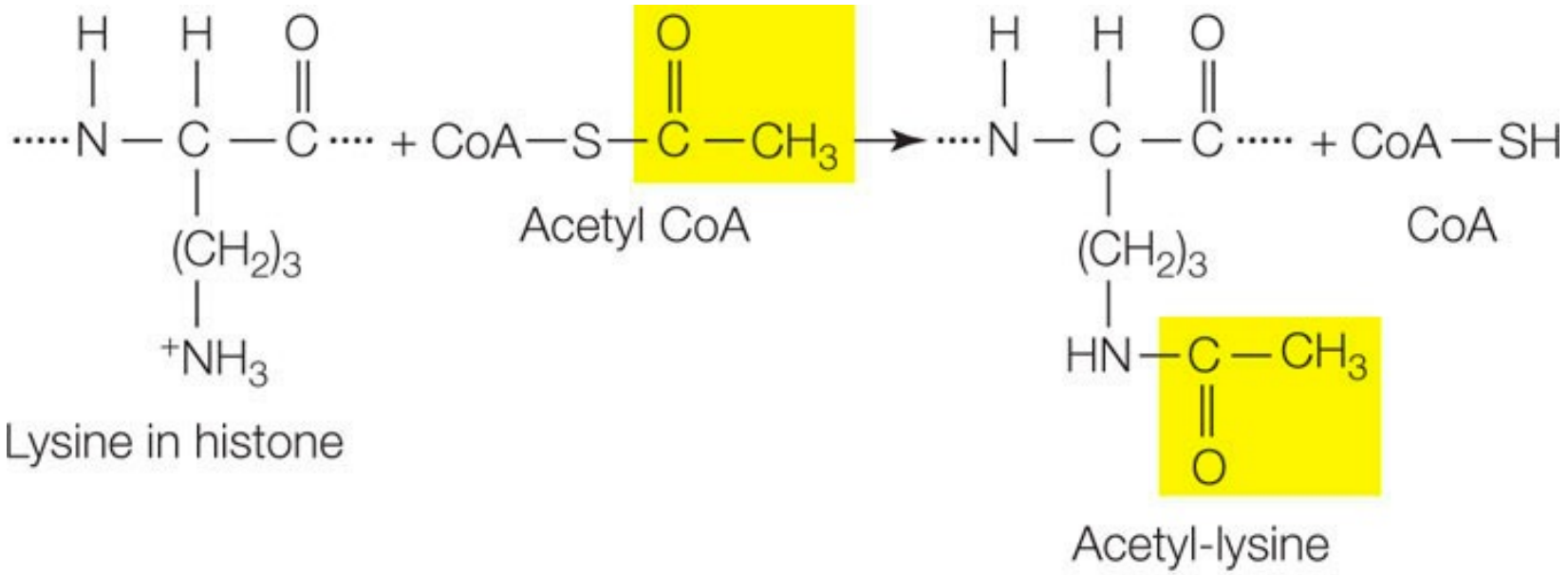


Modification of histone proteins affects chromatin structure and transcription

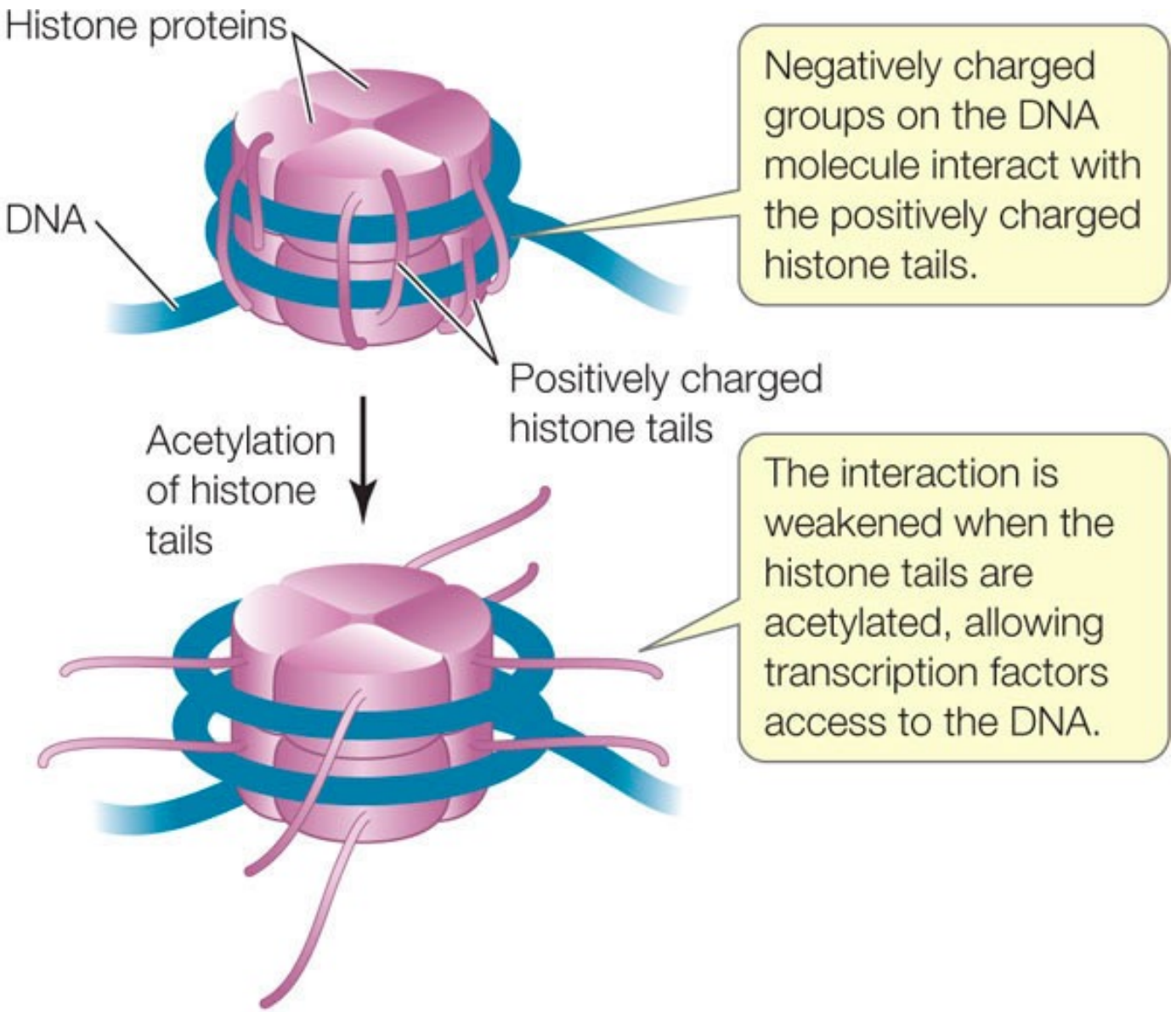
Inactivation du chromosome X

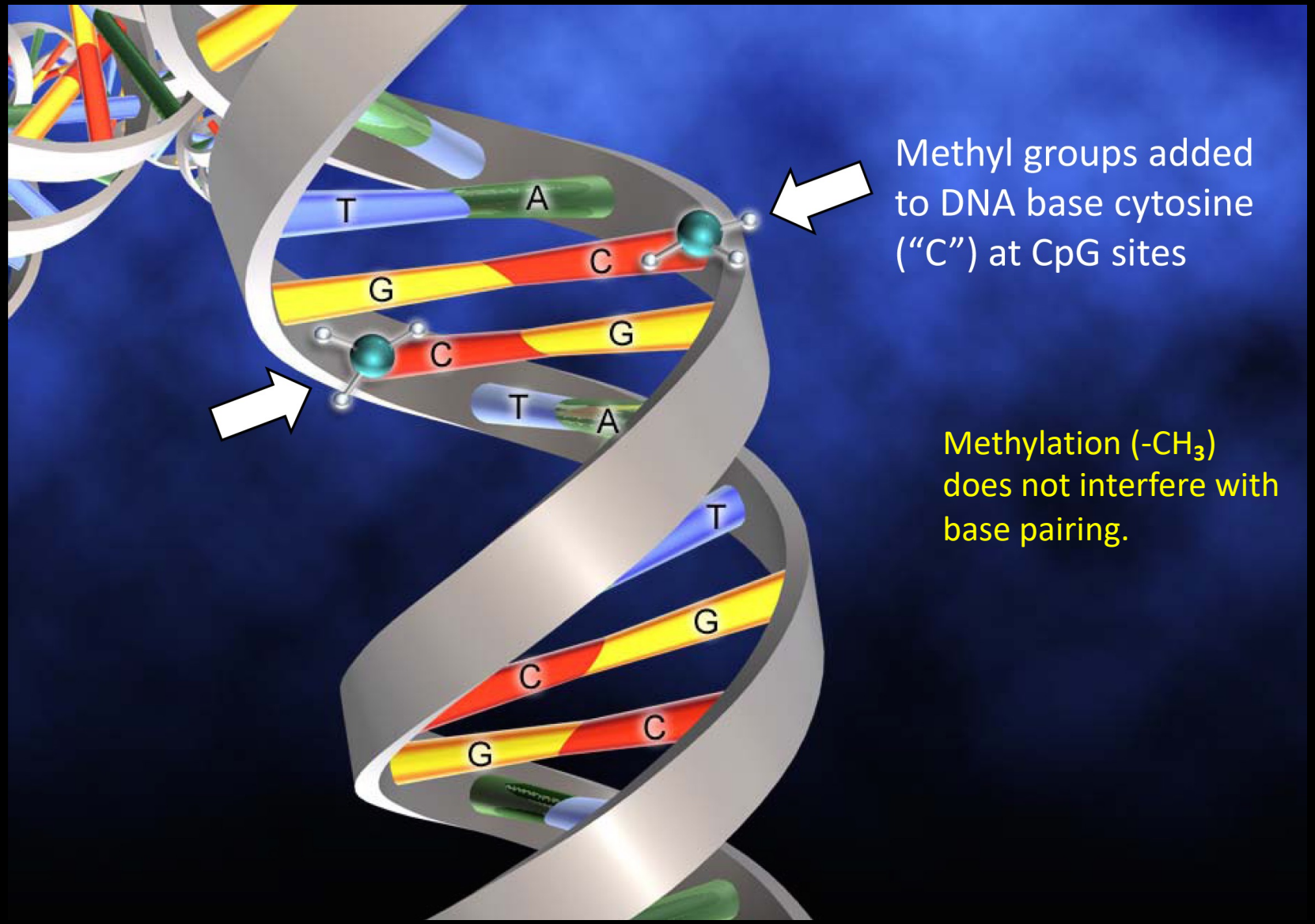


Acetylation catalyzed by an enzyme



Epigenetic Remodeling of Chromatin for Transcription

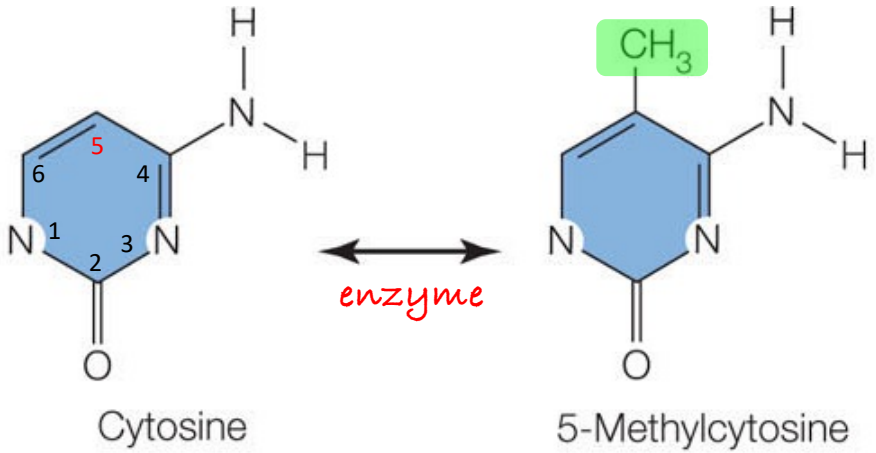




Methyl groups added to DNA base cytosine ("C") at CpG sites

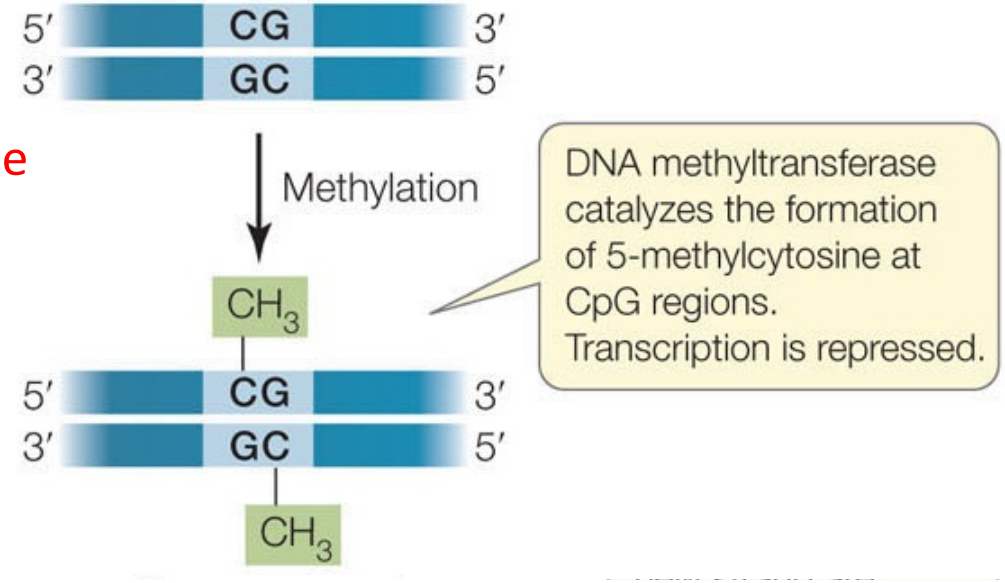
Methylation ($-CH_3$) does not interfere with base pairing.

DNA methylation affects transcription.



In **eukaryotes**, only cytosine is methylated.

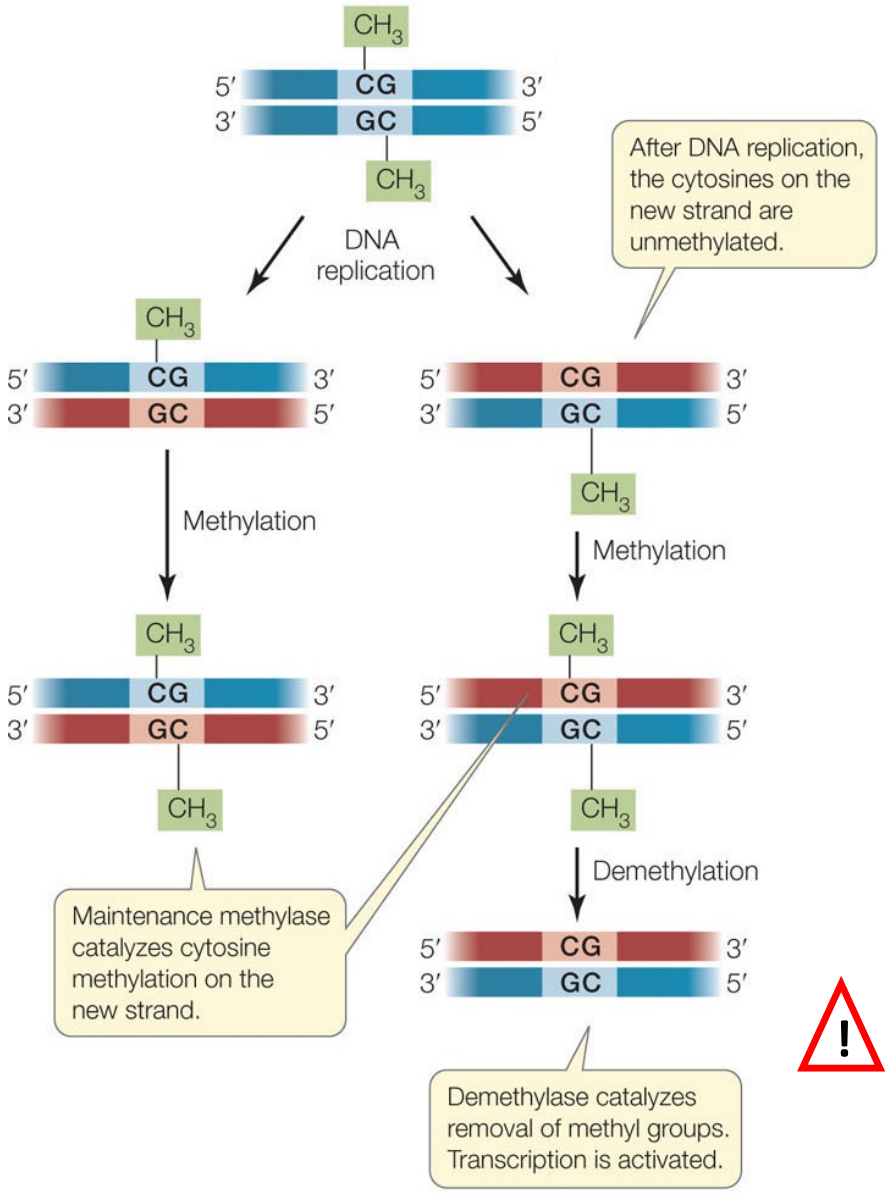
The enzyme DNA methyltransferase recognizes 5'-CG-3' (not only C)



Hemimethylated DNA:

- one strand methylated
- the complementary strand not methylated

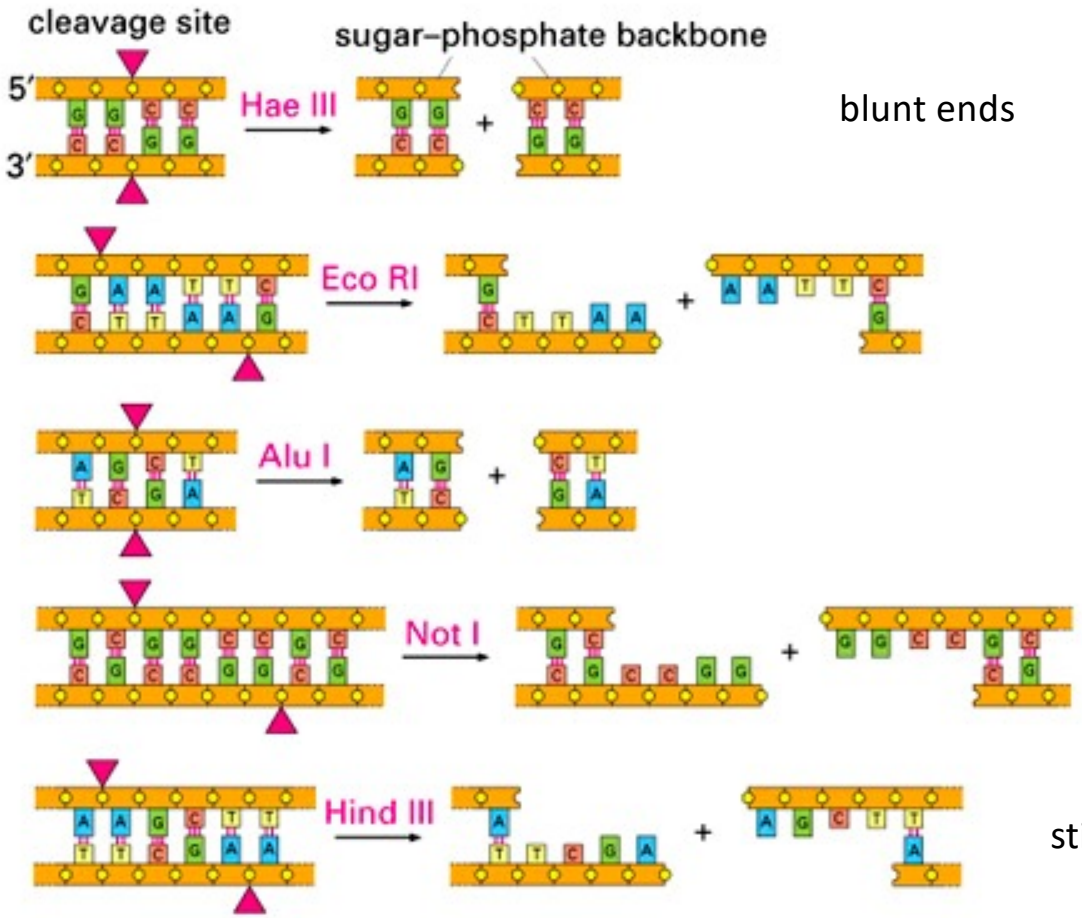
DNA methylation is conserved after replication



DNA polymerase accepts only CTP, not methylated C (actually ^{m}CTP does not exist) The novel strand is initially not methylated.

As of today, no demethylase has been identified !! Still a mystery.

DNA can be cut by restriction nucleases



blunt ends

rare cutter

sticky ends

- cut double-stranded DNA
- at particular sites: recognition sites
- highly specific sequences of
  4 nucleotides: frequent cutters
  6 nucleotides: medium cutters
  8 nucleotides: rare cutters
- from bacteria; defense mechanism against phages

Figure 10-4 Essential Cell Biology, 2/e. (© 2004 Garland Science)

Isoschizomeres

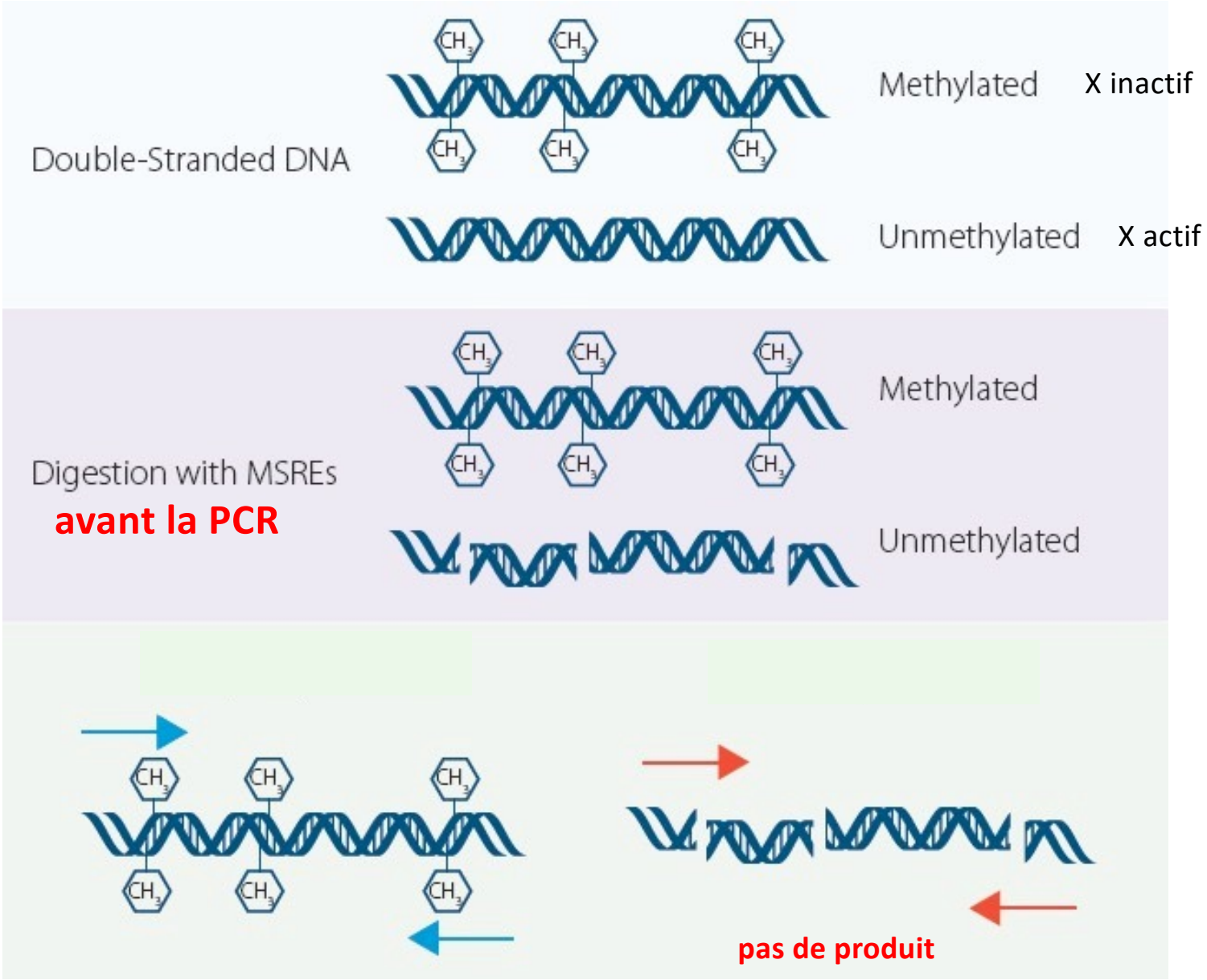
	cut	no cut
Hpa II recognizes	5’- C C G G – 3’ 3’- G G C C – 5’	5’- C ^{m}C G G – 3’ 3’- G G ^{m}C C – 5’
Msp I recognizes	5’- C C G G – 3’ 3’- G G C C – 5’	5’- C ^{m}C G G – 3’ 3’- G G ^{m}C C – 5’
	cut	cut

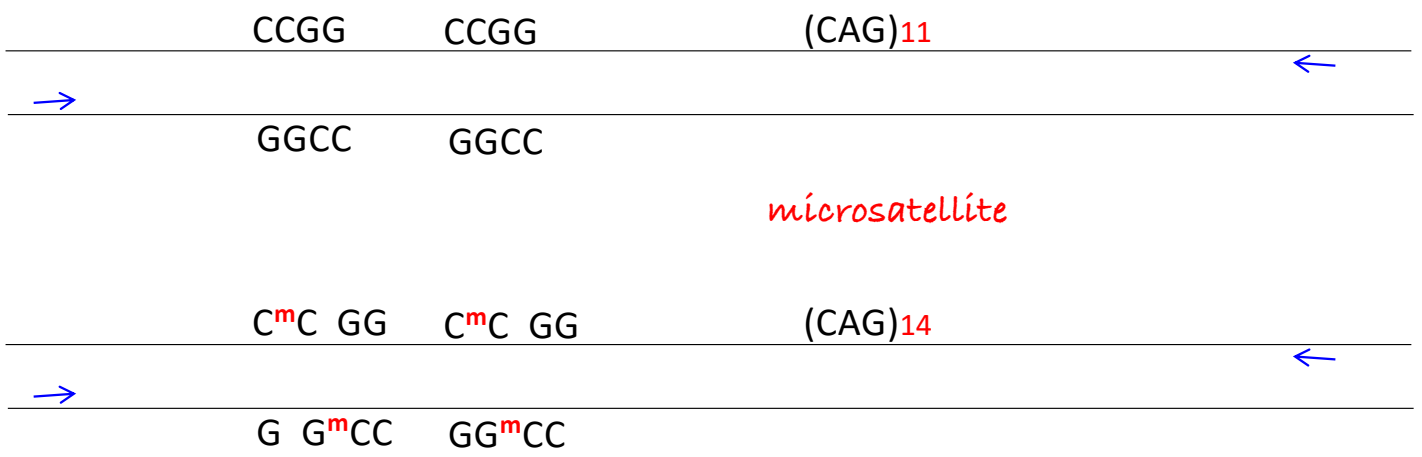
Hpa II and Msp I recognize the same restriction site : they are isoschizomeres.

However there is one important difference :

Hpa II is **sensitive** to DNA methylation

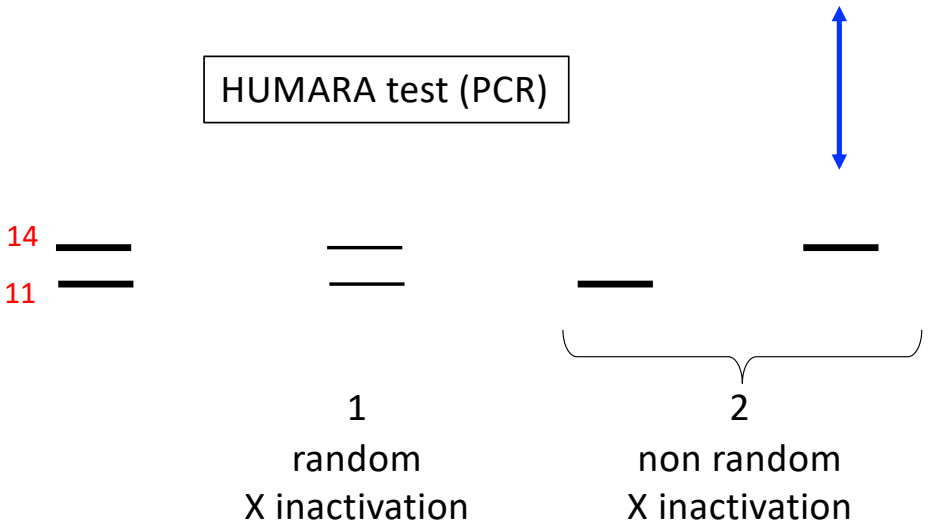
Msp I is **insensitive** to DNA methylation


Double-Stranded DNA
Methylated
X inactif
Unmethylated
X actif
Digestion with MSREs
avant la PCR
Methylated
Unmethylated
pas de produit

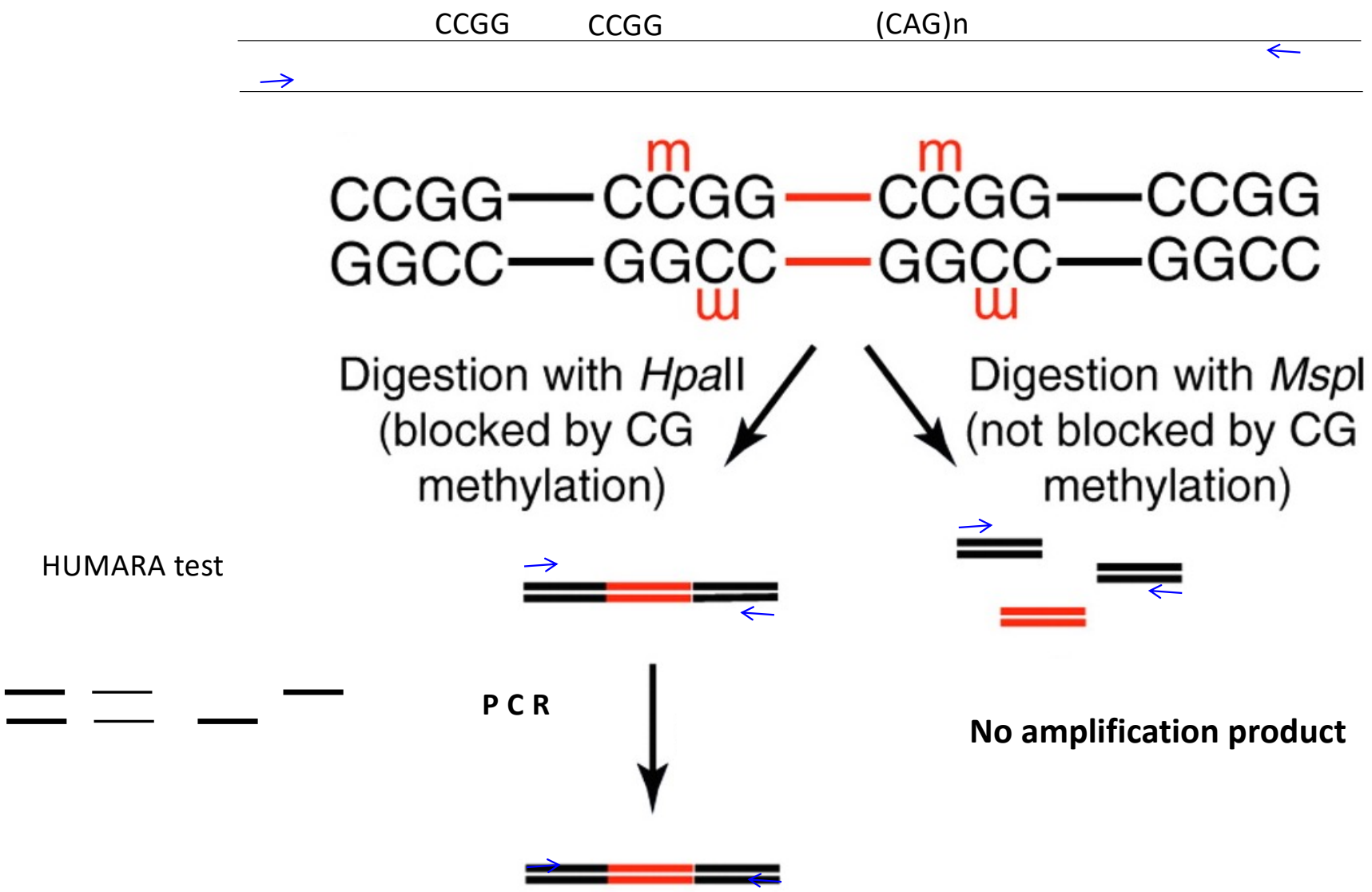


The active X
is not methylated

The inactive X
is methylated

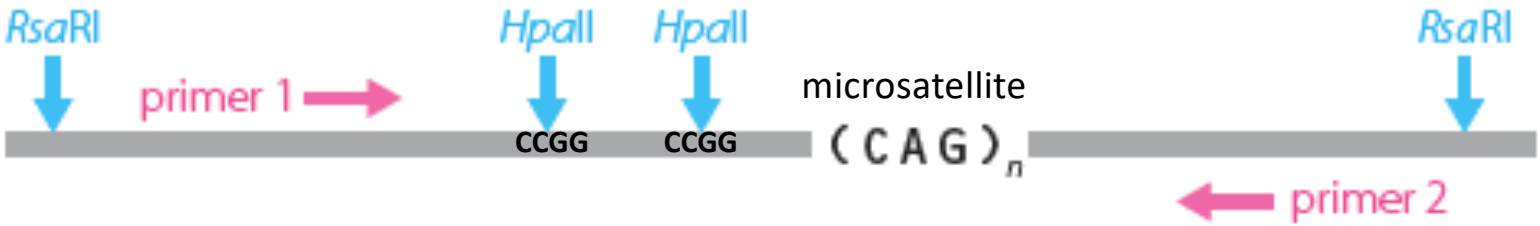


Only the DNA from the **inactive X** can be amplified by PRC.


CCGG
CCGG
(CAG)n
m
m
CCGG—CCGG—CCGG—CCGG
GGCC—GGCC—GGCC—GGCC
Digestion with HpaII (blocked by CG methylation)
Digestion with MspI (not blocked by CG methylation)
HUMARA test
P C R
No amplification product

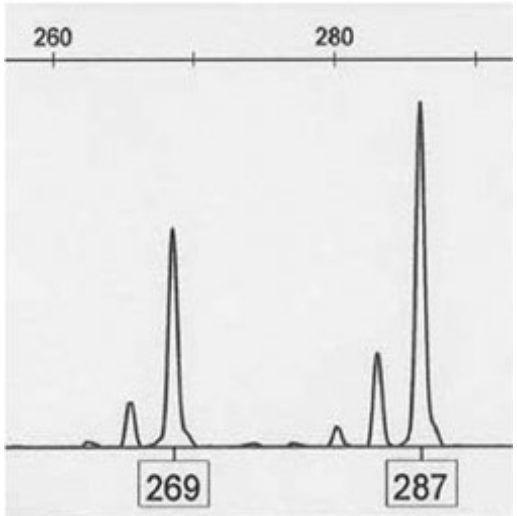
Un microsatellite localisé sur le chromosome X

(gène codant le récepteur pour les androgènes)



Produit de la PCR (C A G)n

Femme hétérozygote pour le microsatellite



Notez :

- 2 pics principaux
- des pics mineurs (glissade/bégaiement)