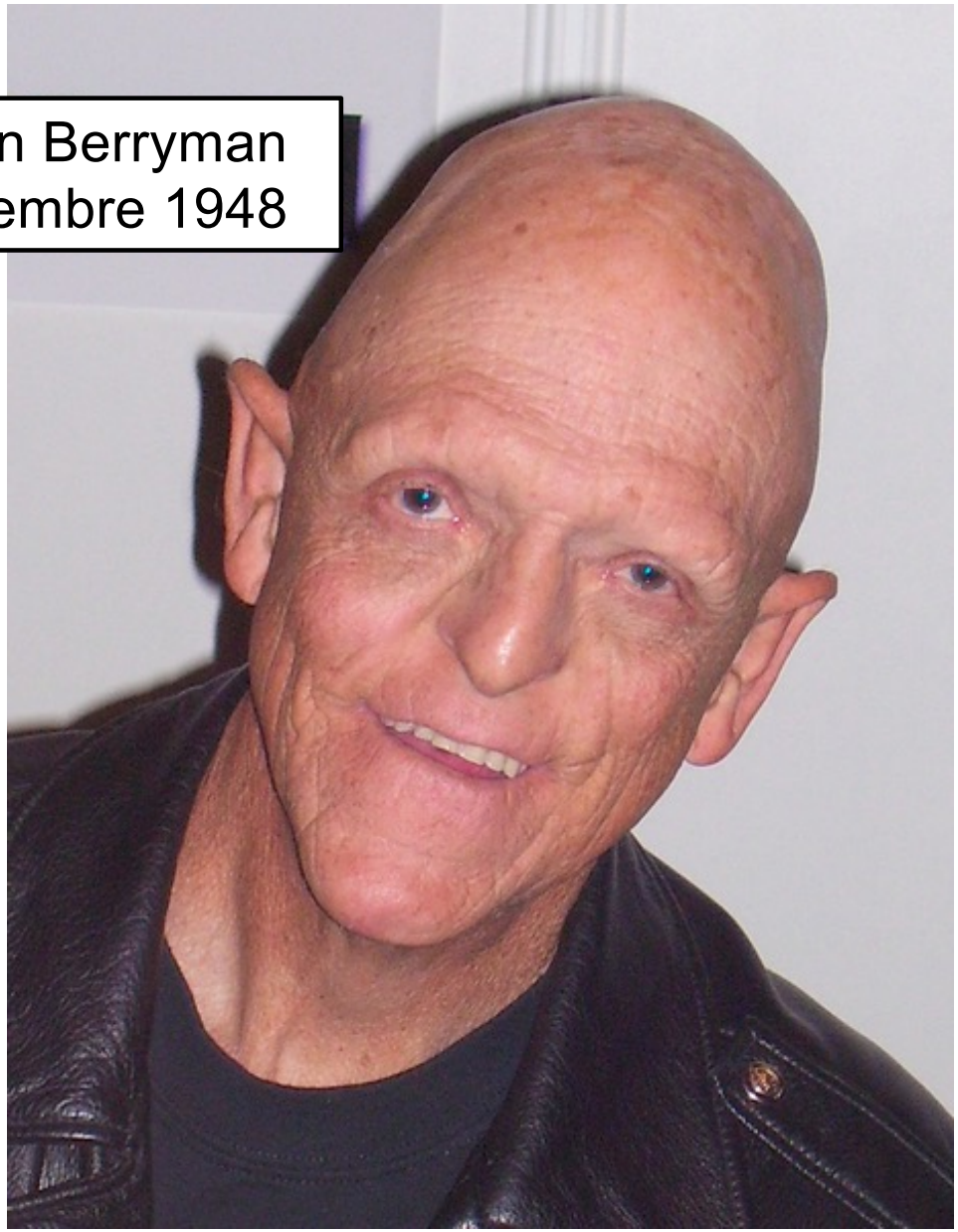
Michael John Berryman
né le 4 septembre 1948



X-linked
hypoidrotic
ectodermal
dysplasia

Acteur :
Rôle dans des film d'horreur

Un garçon
âgé de 13 mois

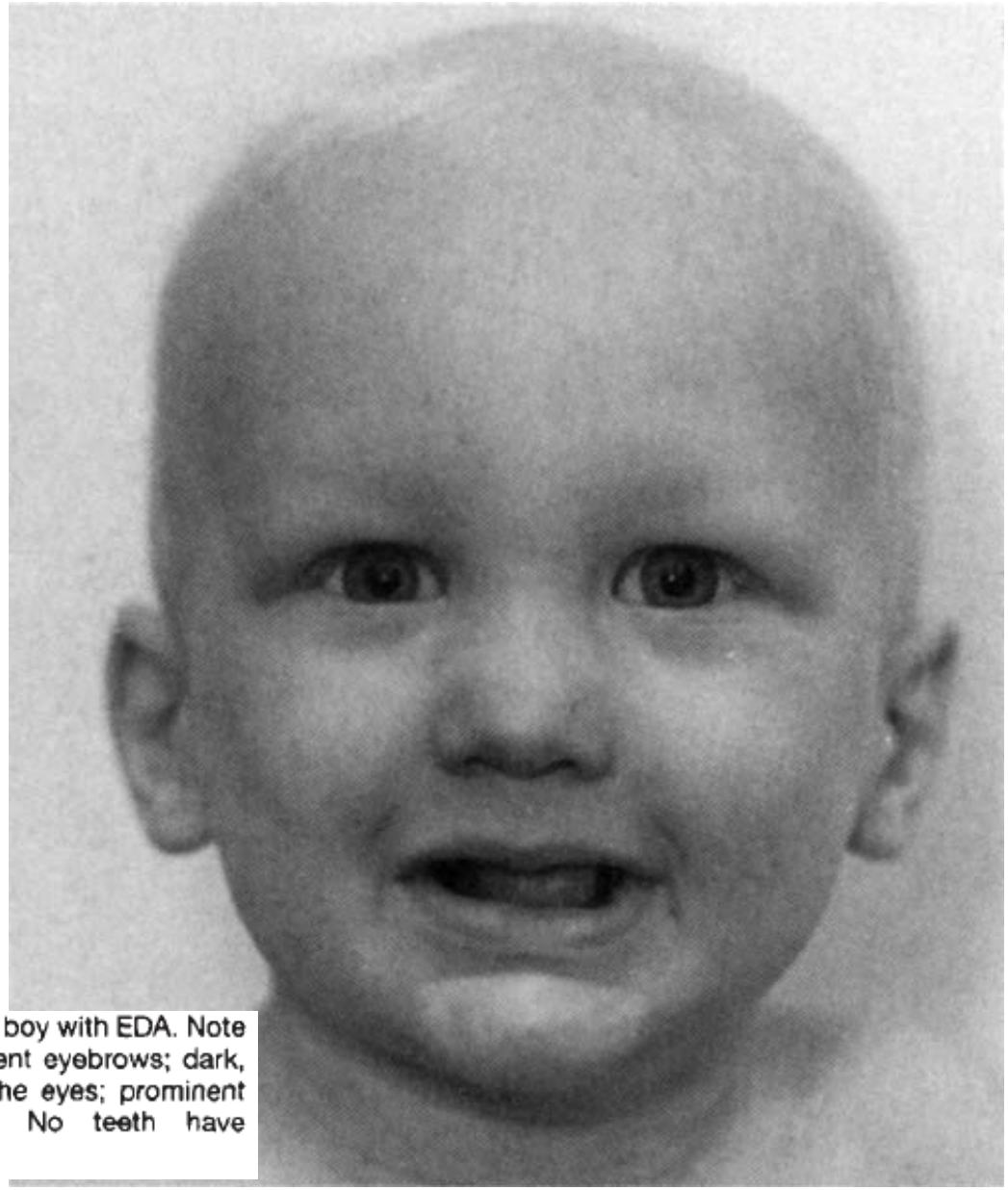


Fig. 1 A 13-month-old boy with EDA. Note sparse, thin hair; absent eyebrows; dark, wrinkled skin under the eyes; prominent forehead; dry skin. No teeth have appeared.

X-linked
hypoidrotic
ectodermal
dysplasia

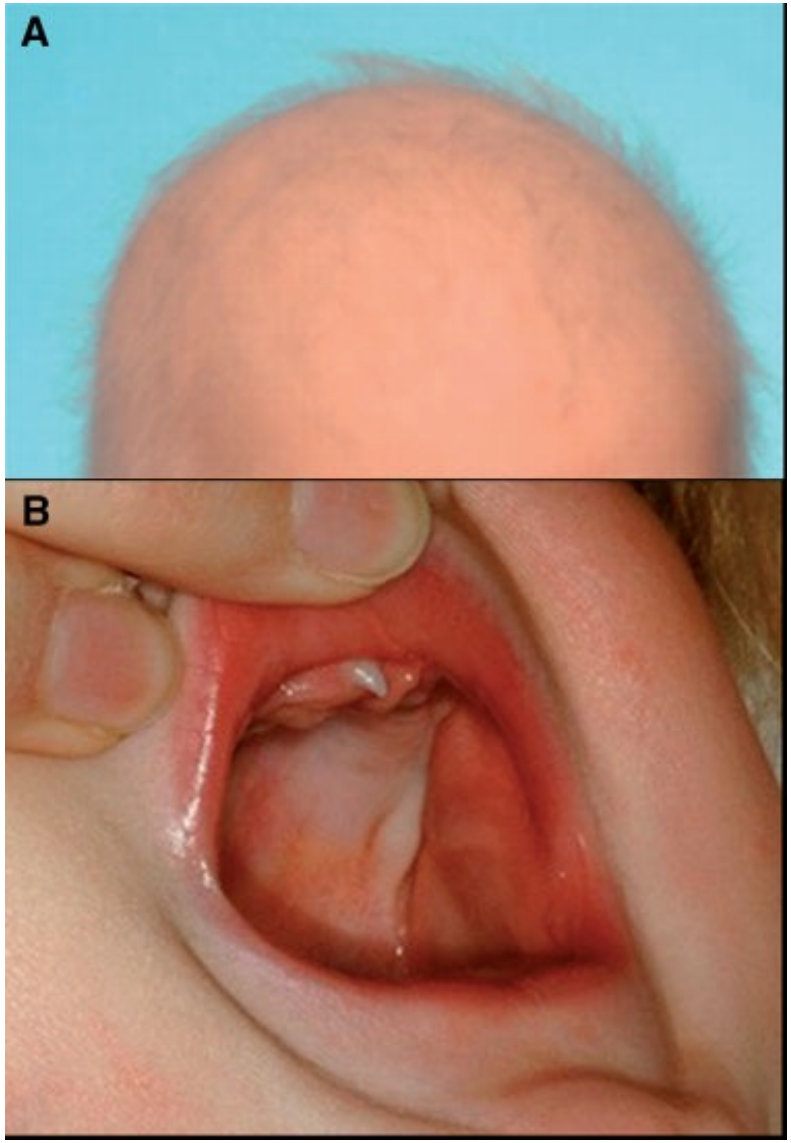
Un cas exceptionnel :

Une ***fille*** atteinte de

dysplasie ectodermique hypohidrotique

(Ni le père ni la mère ne sont atteints de cette maladie)

Une **fille** avec une atteinte sévère : problème avec l'inactivation du X



Hypotrichose

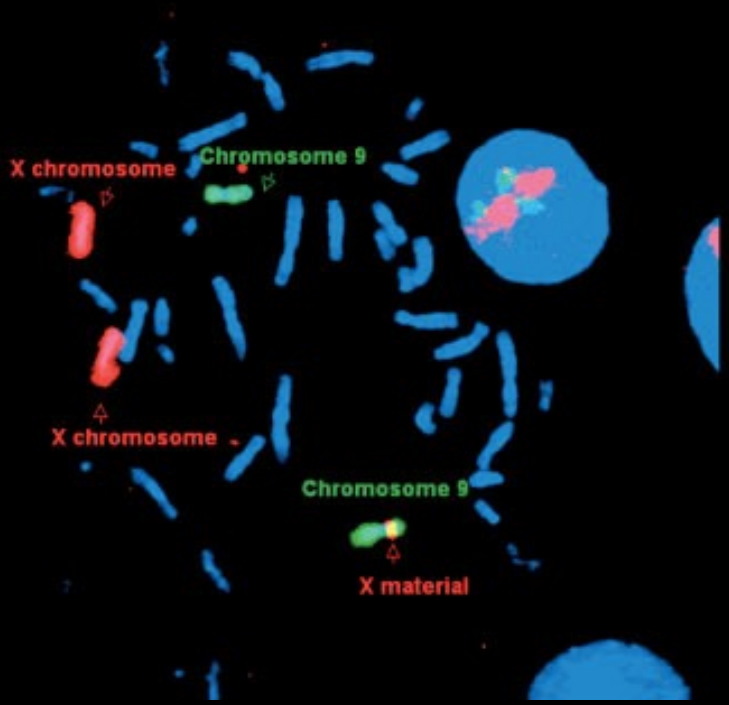
Hypodontie

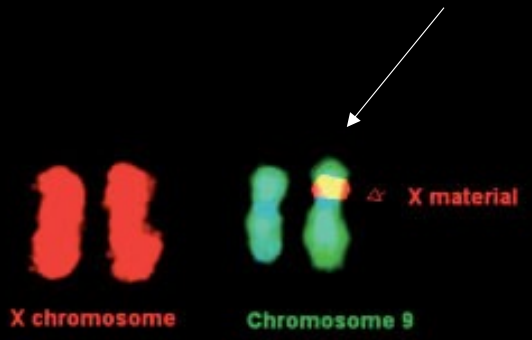
ØRSTAVIK ET AL.

(A) Hair and (B) teeth of patient at age 2 1/2 years.

Le X normal (maternel) est toujours inactivé
Le X anormal (paternel) n'est jamais inactivé

Ce chromosome 9 est plus long que l'autre

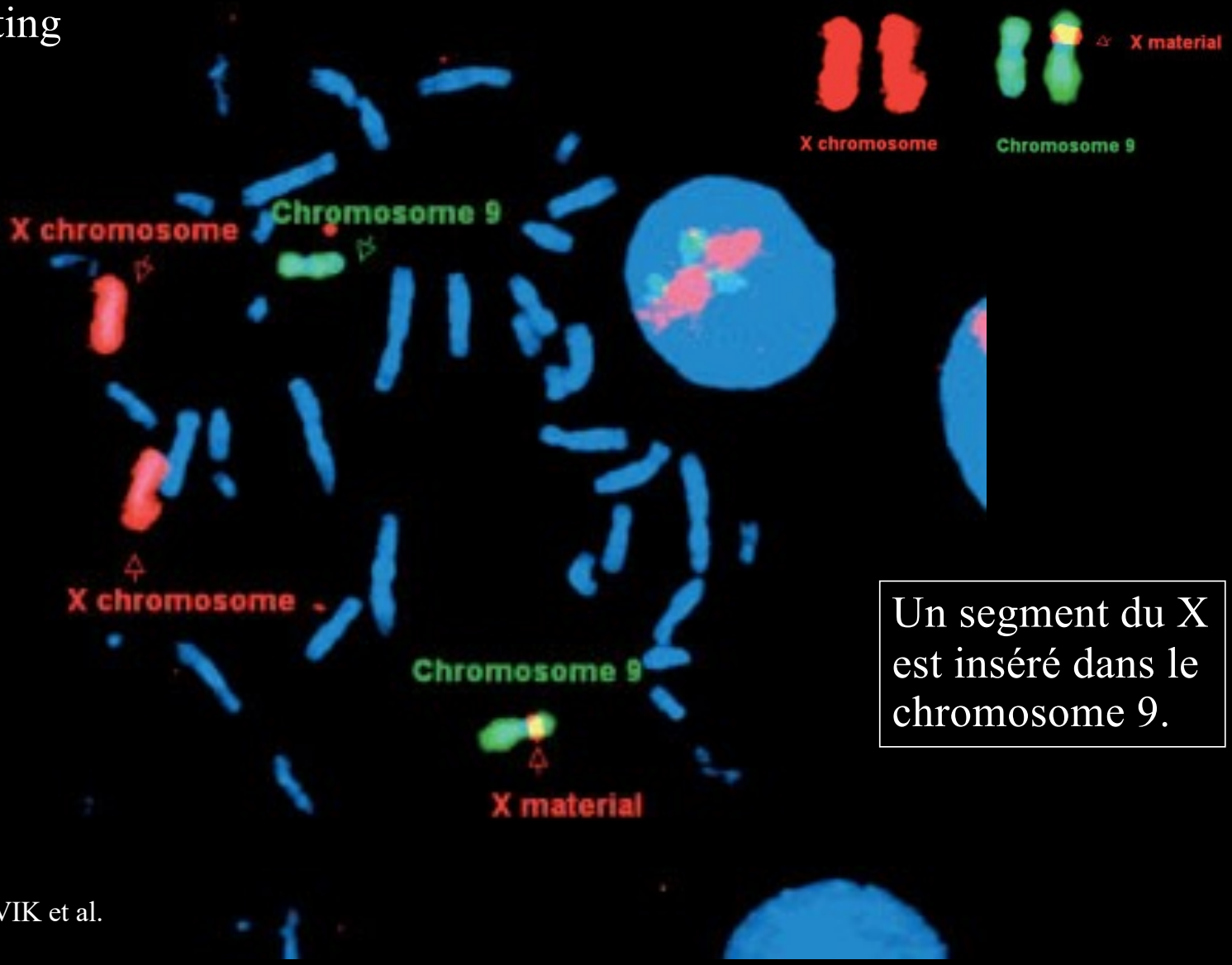




Chromosome X peint en rouge
Chromosome 9 peint en vert

ØRSTAVIK et al.

painting

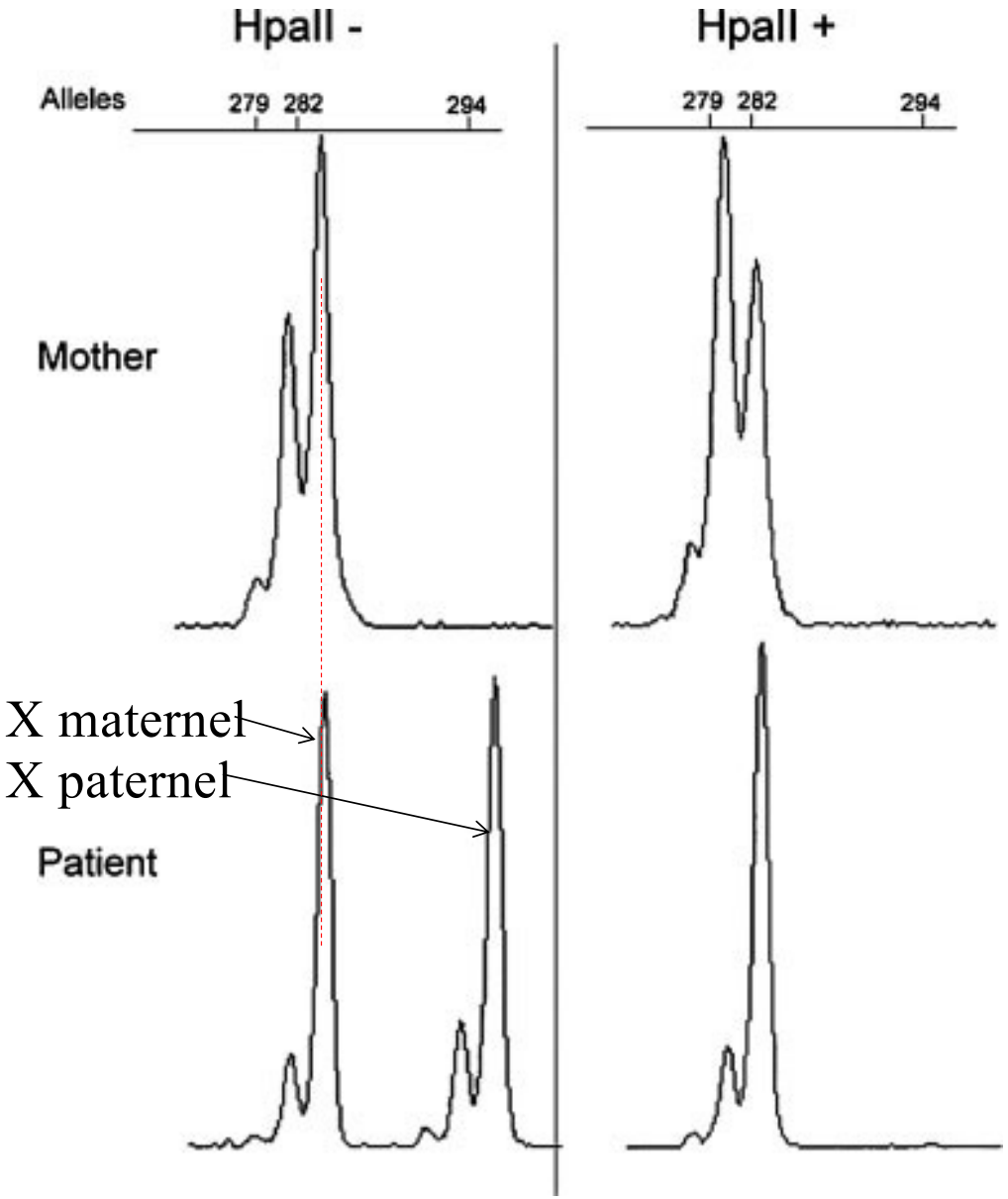


Un segment du X est inséré dans le chromosome 9.

ØRSTAVIK et al.

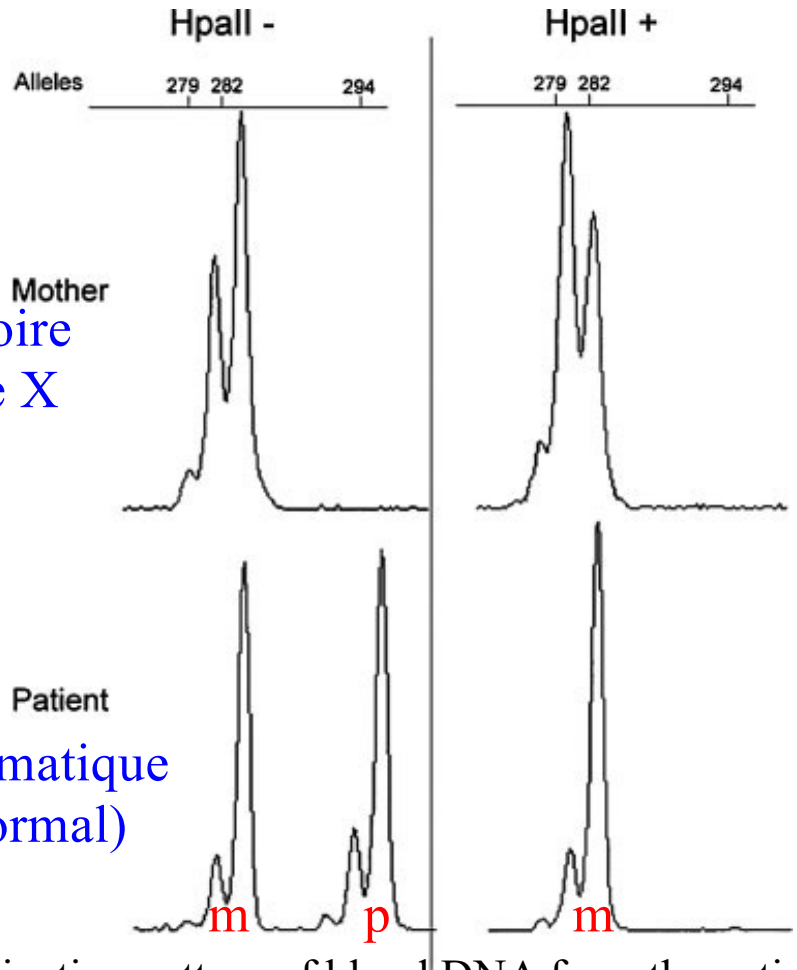
PCR :
Trinucléotide dans exon 1 du gène Récepteur aux androgènes

Test HUMARA



Le X paternel est toujours actif
Le X maternel n'est jamais actif

ØRSTAVIK ET AL.



Inactivation du X chez la mère :
50 / 50 donc normale

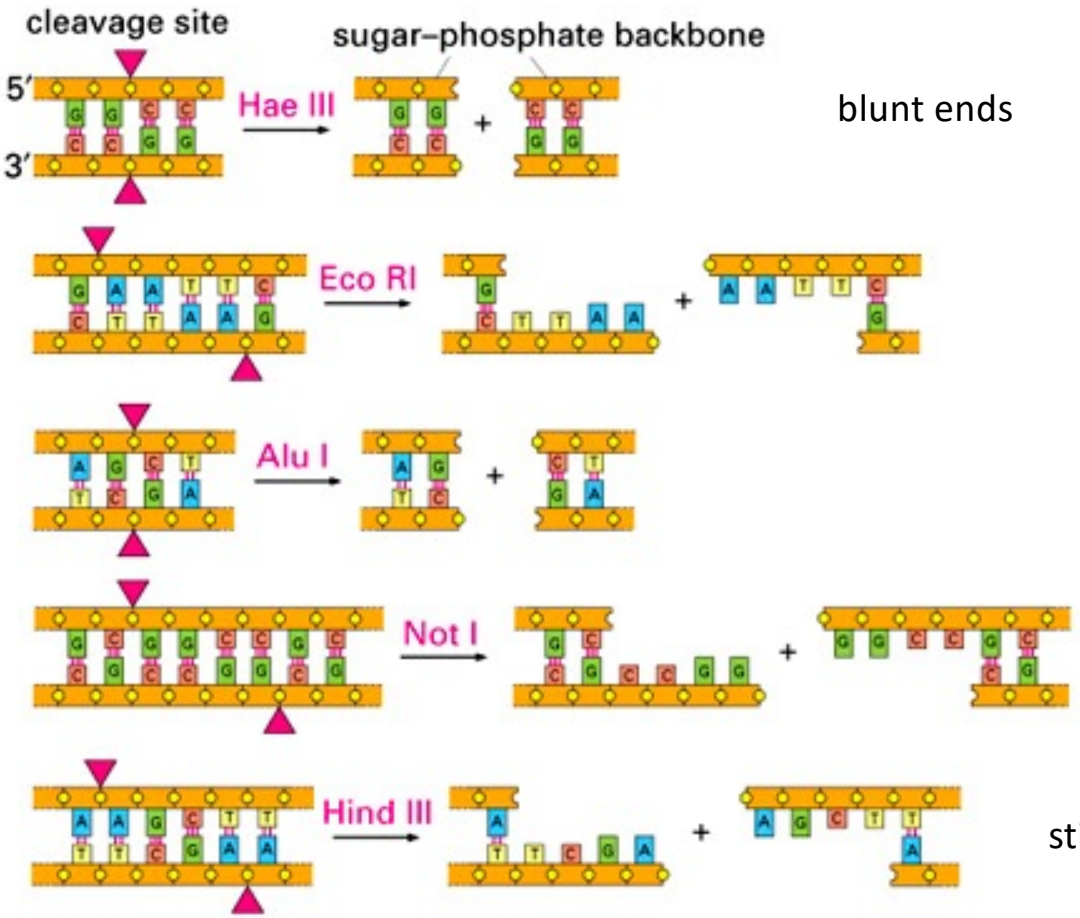
Inactivation aléatoire
d'un chromosome X

Inactivation systématique
du X maternel (normal)

Le chromosome X
digéré par HpaII
ne peut plus être
amplifié.

X chromosome inactivation pattern of blood DNA from the patient and her mother. Note PCR product from the inactive maternal X chromosome only after digestion with the **methylation sensitive enzyme HpaII**. The patient had a completely skewed X-inactivation with the paternal X as the active X in all cells. Mother had a random X-inactivation.

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.

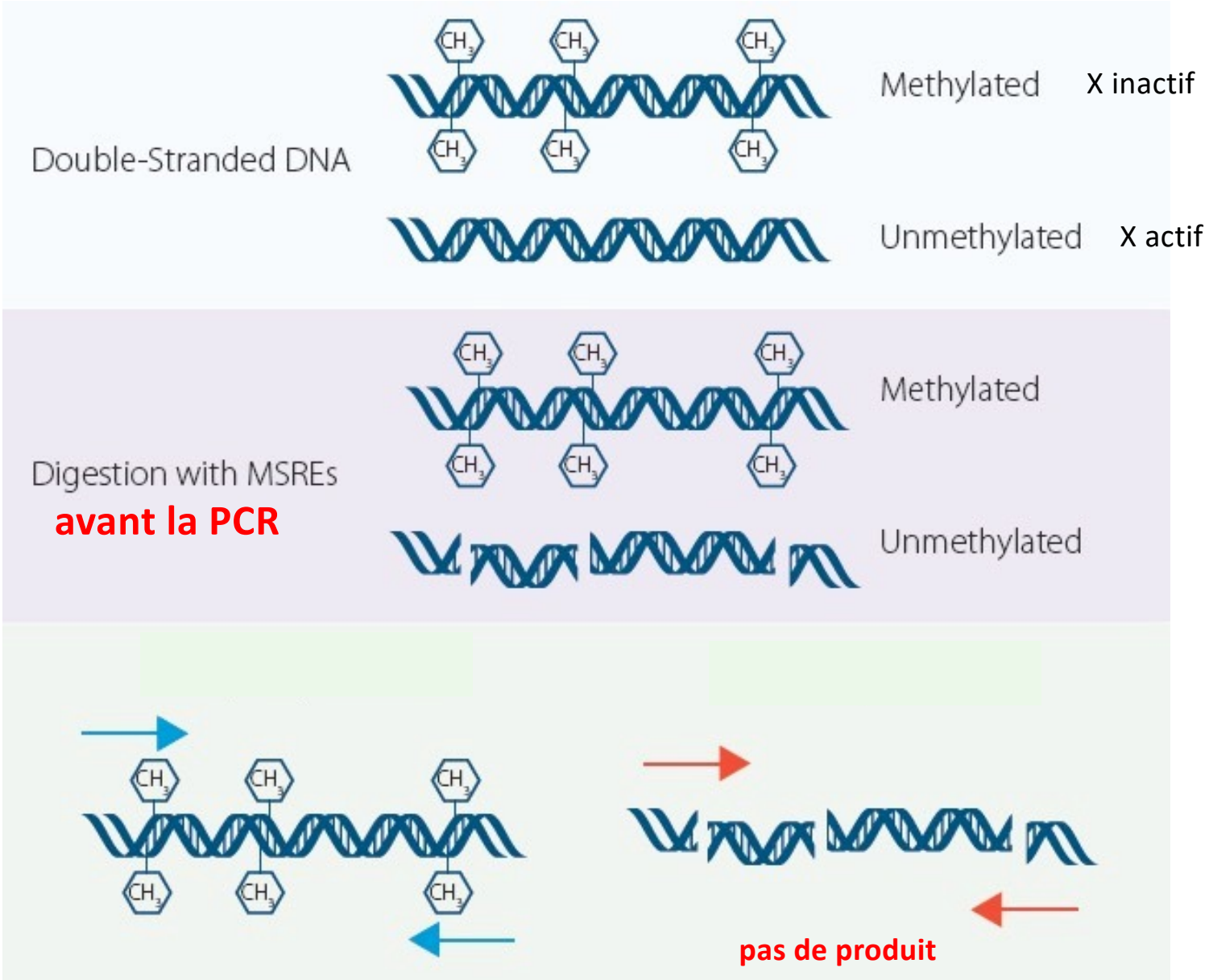
However there is one important difference :

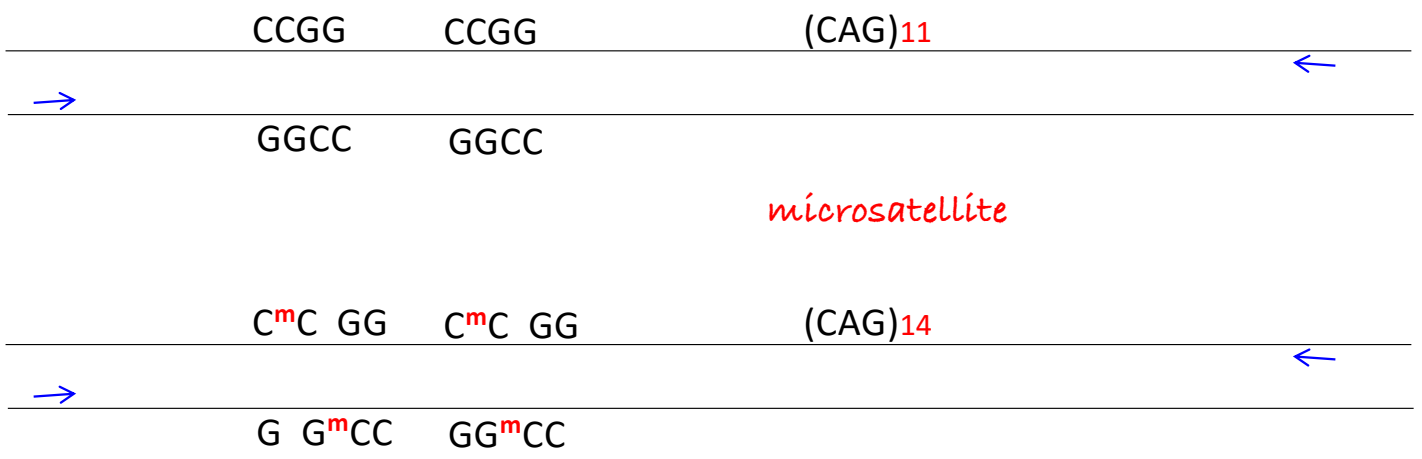
Hpa II is **sensitive** to DNA methylation

Msp I is **insensitive** to DNA methylation

HUMARA

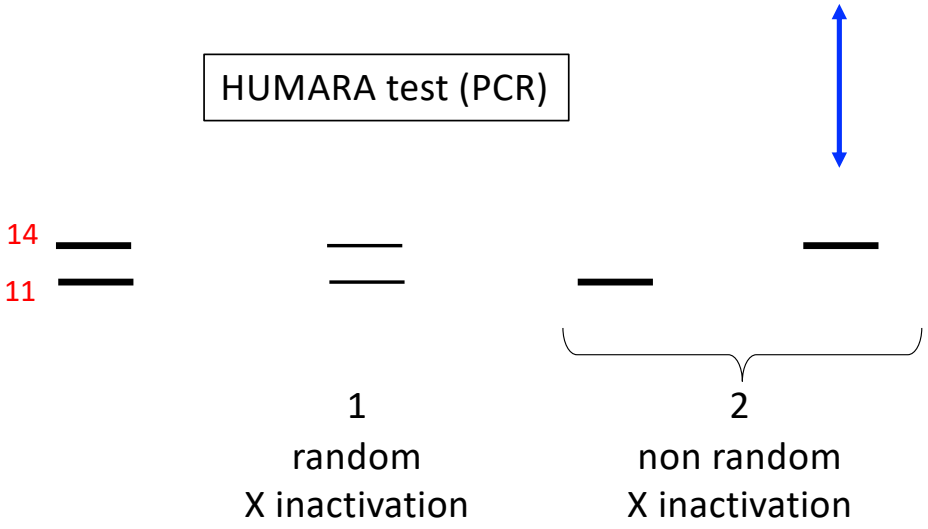
Methyl
Sensitive
Restriction
Enzyme



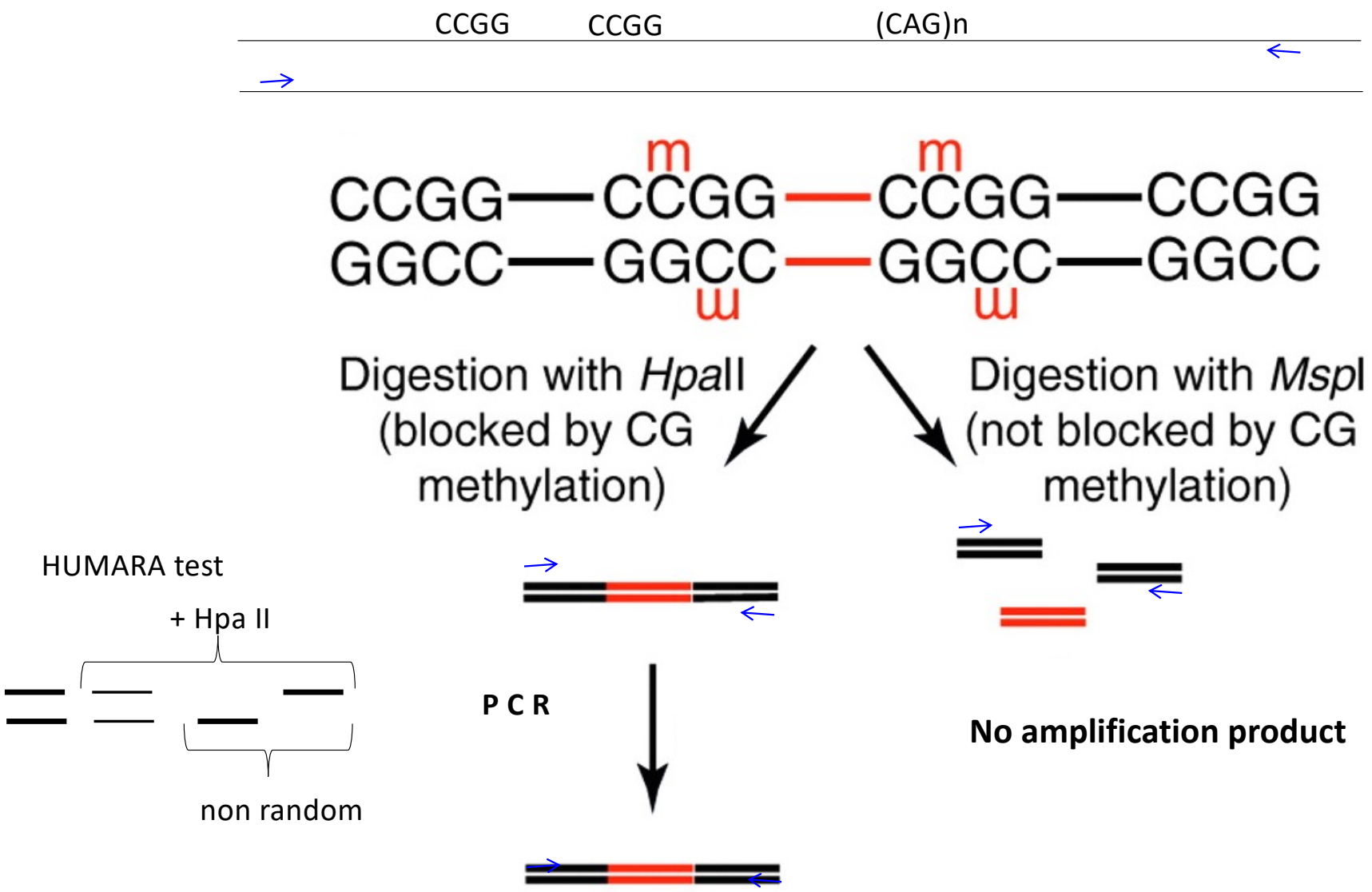


The active X
is not methylated

The inactive X
is methylated

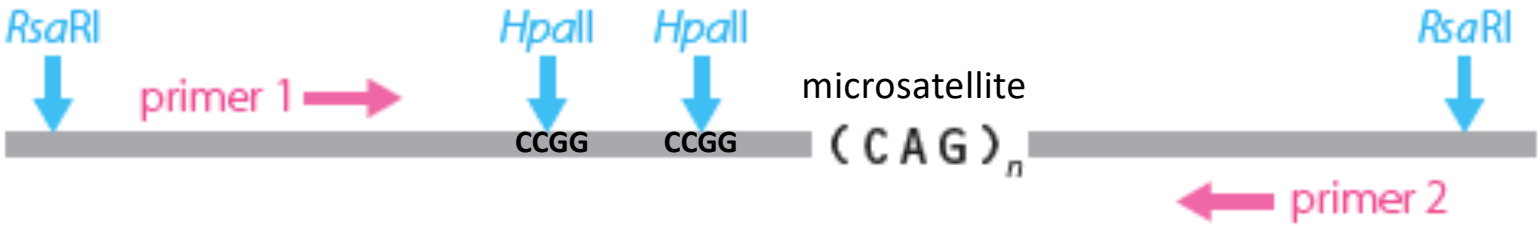


Only the DNA from the **inactive X** can be amplified by PRC.


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
+ Hpa II
non random
P C R
No amplification product

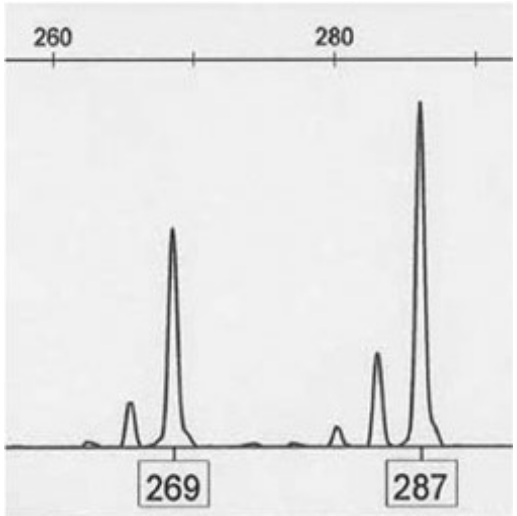
Un microsatellite localisé sur le chromosome X

(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)

Example of testing

Mother shows non random X inactivation

Patient shows non random X inactivation

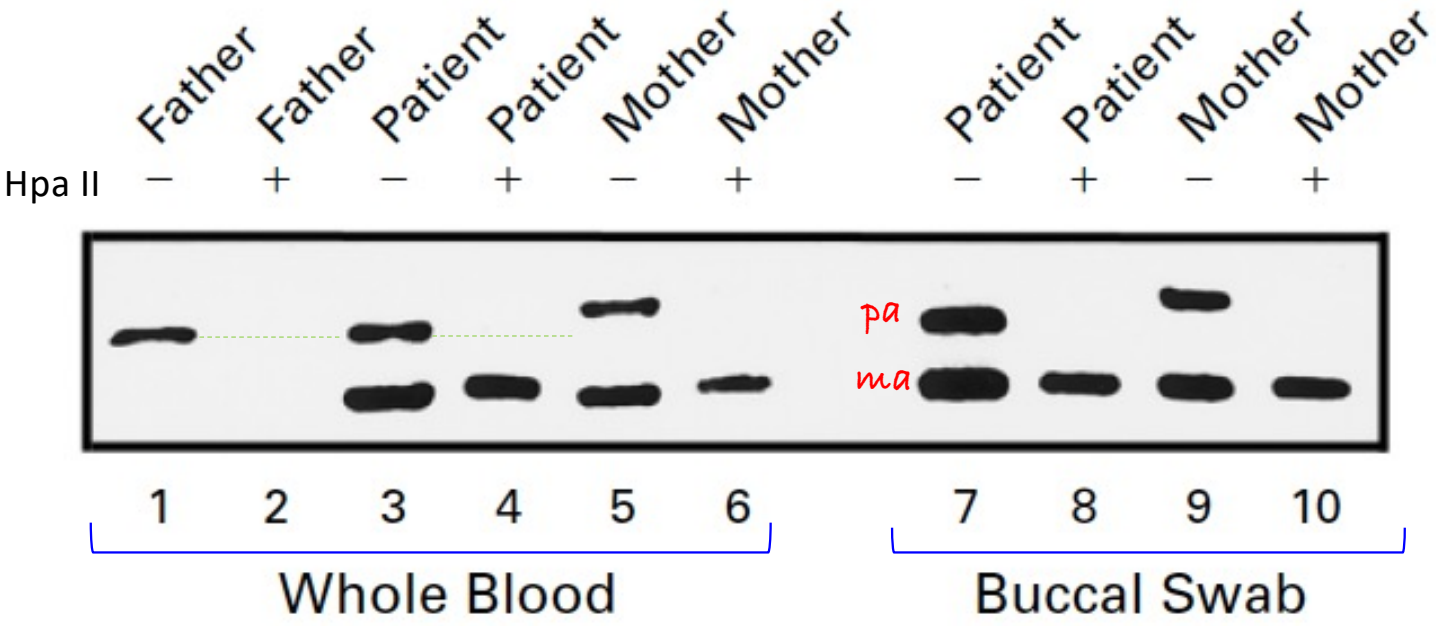
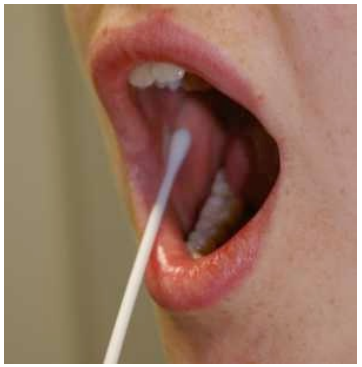


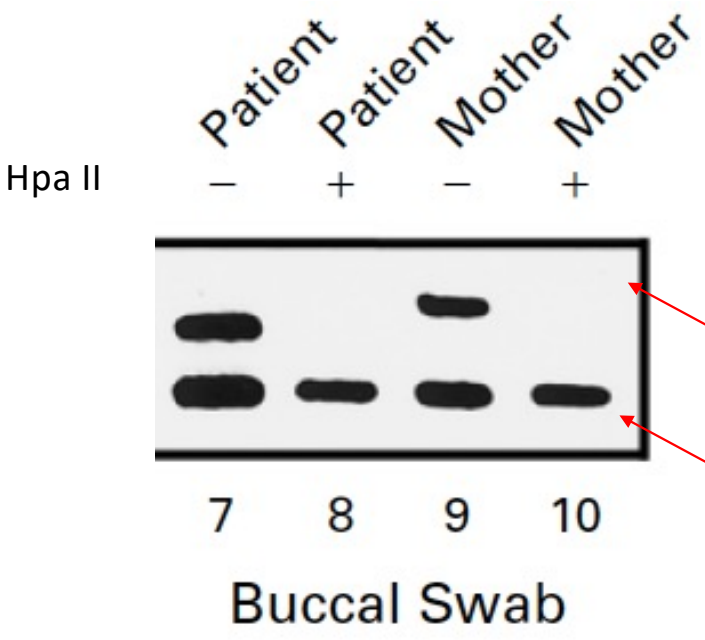
Figure 1. Analysis of the Pattern of X-Chromosome Inactivation in the Patient and Her Parents.

DNA was extracted from whole blood or oral mucosal cells from the patient and her parents and amplified by PCR with specific primers that flank the *HUMARA* locus (lanes 1, 3, 5, 7, and 9; labeled with a minus sign). In addition, the DNA was digested with the methylation-sensitive enzyme *Hpa*II before PCR amplification (lanes 2, 4, 6, 8, and 10; labeled with a plus sign). The samples were analyzed on 3 percent agarose gel and stained with ethidium bromide.



Whole blood and buccal swab give identical results

Hpa II digeston ***before*** PCR



Mother shows
non random
X inactivation

Why ? XIC is mutated

Hypothèse à retenir :
1 des chromosomes X est muté, pas les 2

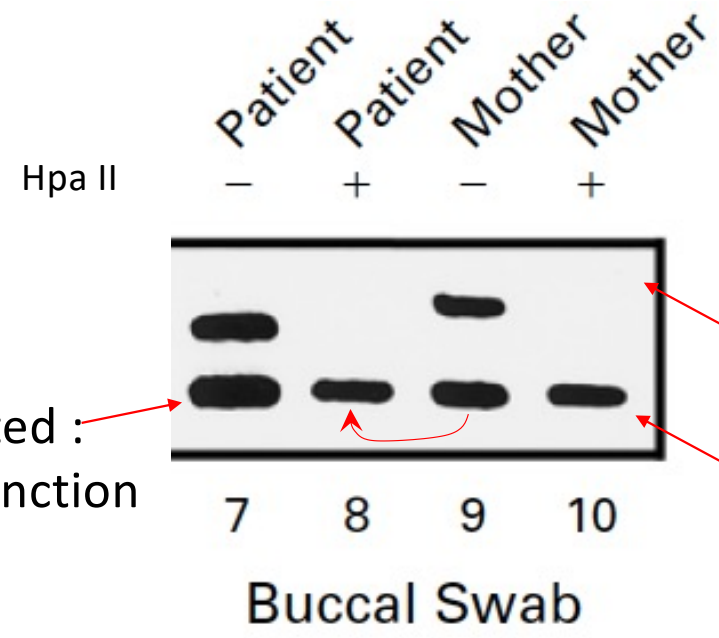
never inactivated

always inactivated

A priori 2 possibilities :

1. Top allele has a **loss-of-function** mutation
2. Bottom allele has a **gain-of-function** mutation

Hpa II digeston ***before*** PCR



XIC mutated :
gain-of-function

never inactivated

always inactivated

Patient shows
non random
X inactivation

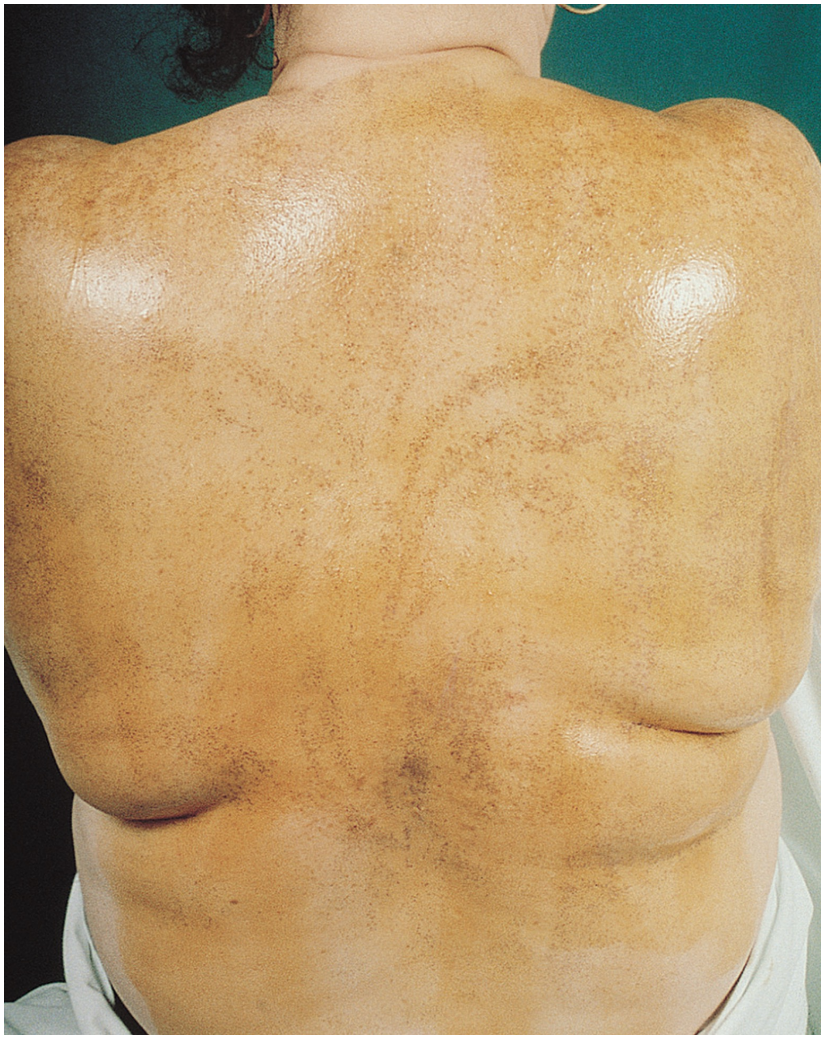
Why ? XIC is mutated

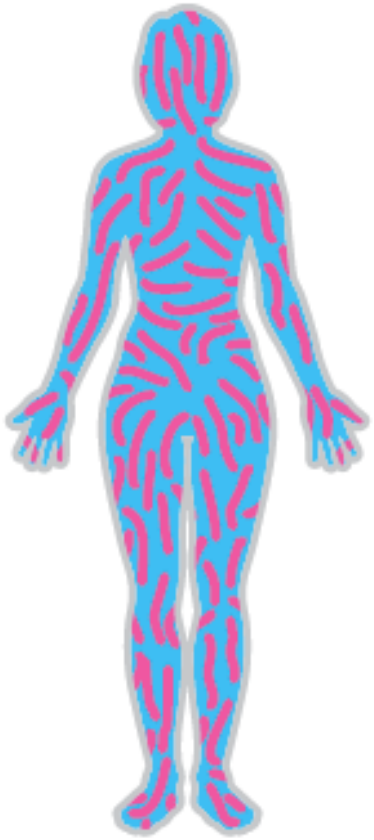
Observation in the patient shows that the mother has a gain-of-function mutation.

2 possibilities :

1. Top allele has a **loss-of-function** mutation
2. Bottom allele has a **gain-of-function** mutation

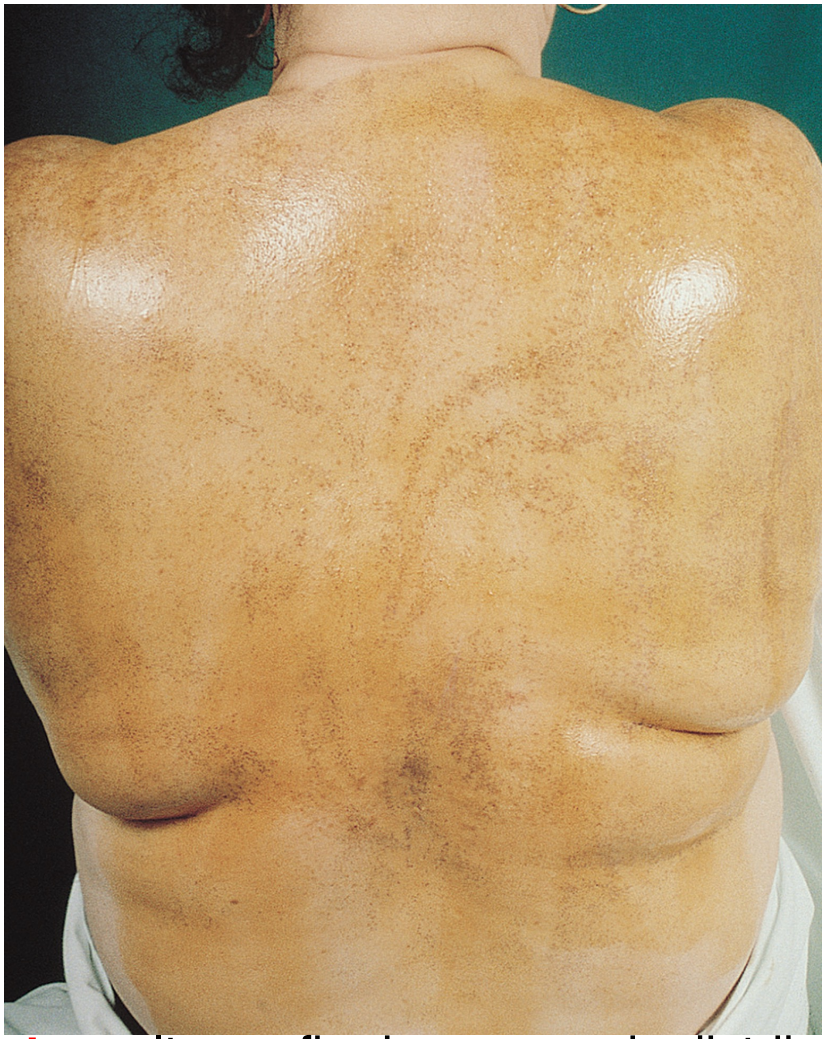
Inactivation d'un chromosome X

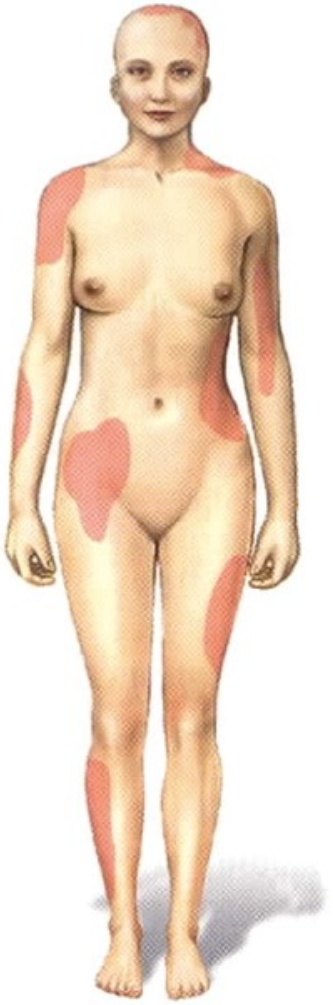




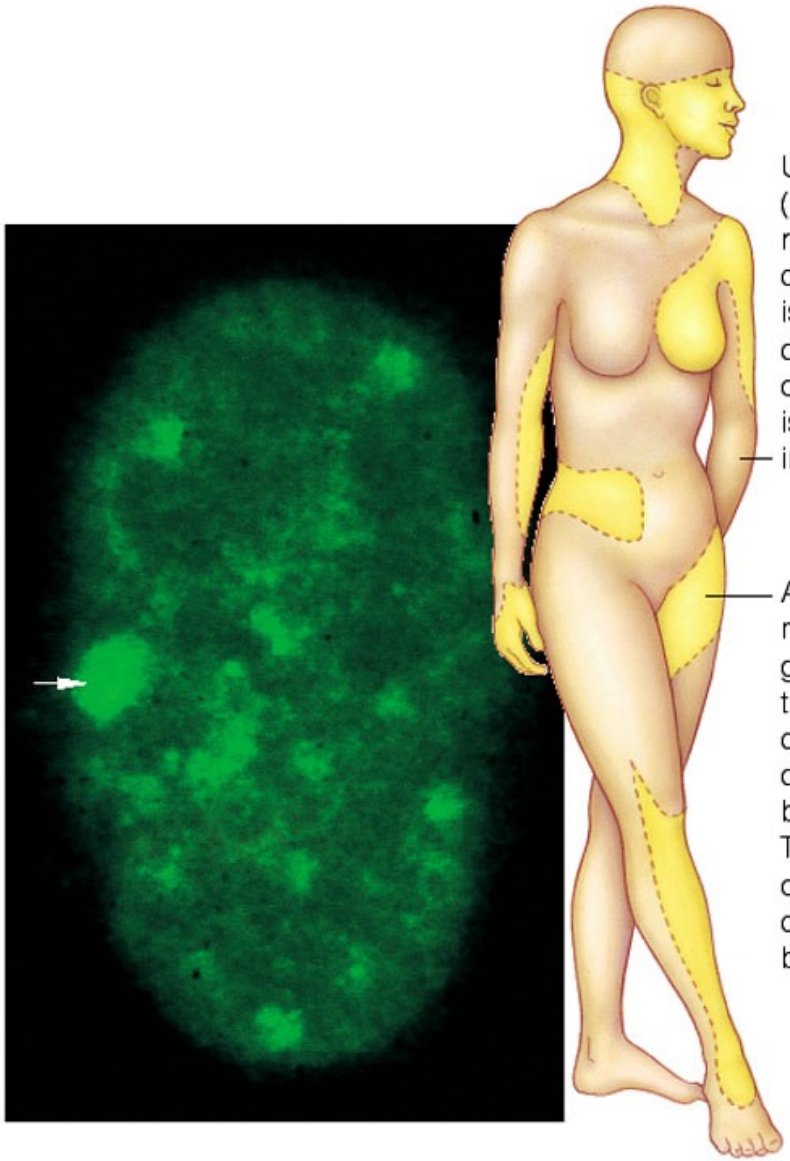
Starch-iodine test results confirming a mosaic distribution of functional sweat glands in a *heterozygous female* carrier of X-linked hypohidrotic ectodermal dysplasia.

Inactivation d'un chromosome X





Starch-iodine test results confirming a mosaic distribution of functional sweat glands in a *heterozygous female* carrier of X-linked hypohidrotic ectodermal dysplasia.

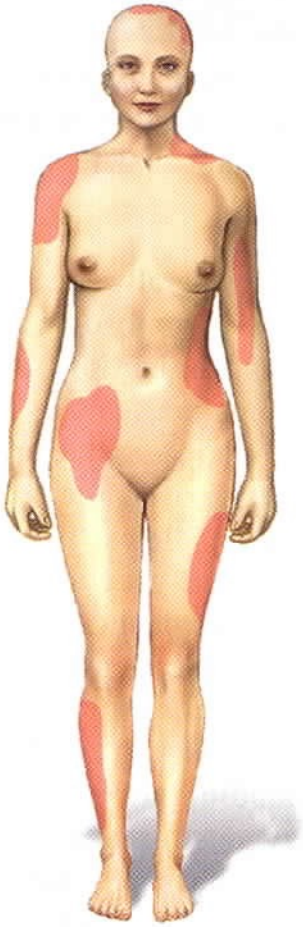


Corpuscule de Barr

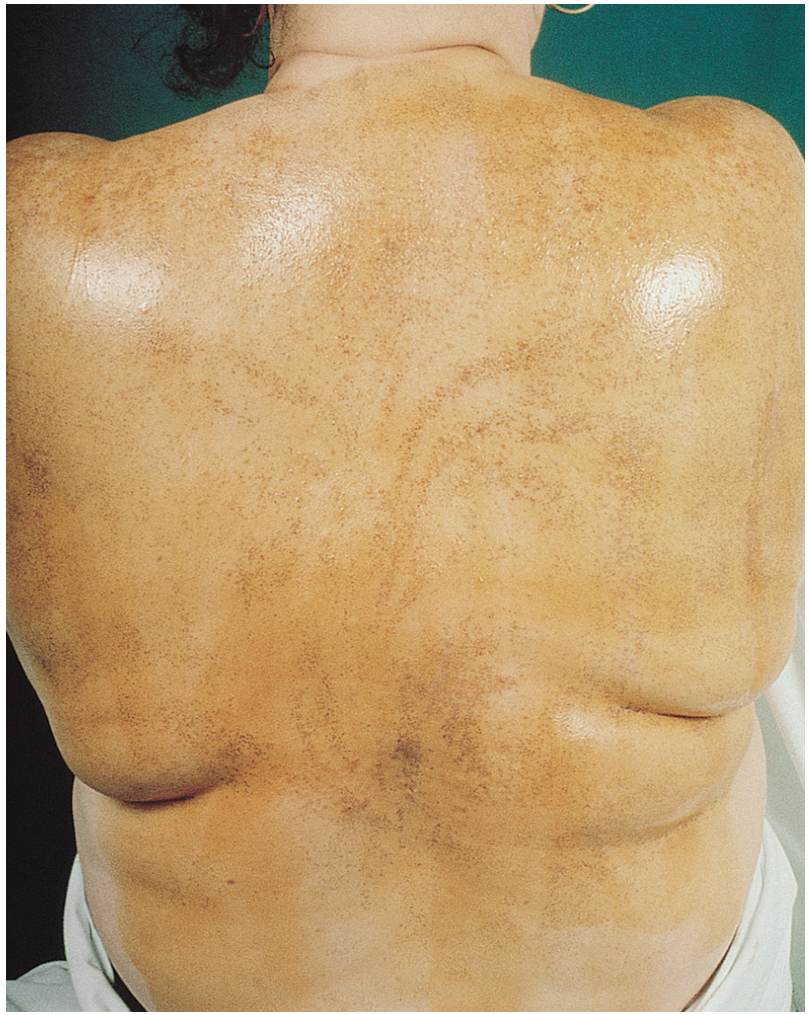
Zone **avec** glandes sudoripares

Zone **sans** glandes sudoripares

Extrapolation ***incorrecte***
des chattes calicos aux femmes hétérozygotes.



Le mosaïcisme cutané humain ressemble à celui des tortoiseshells.



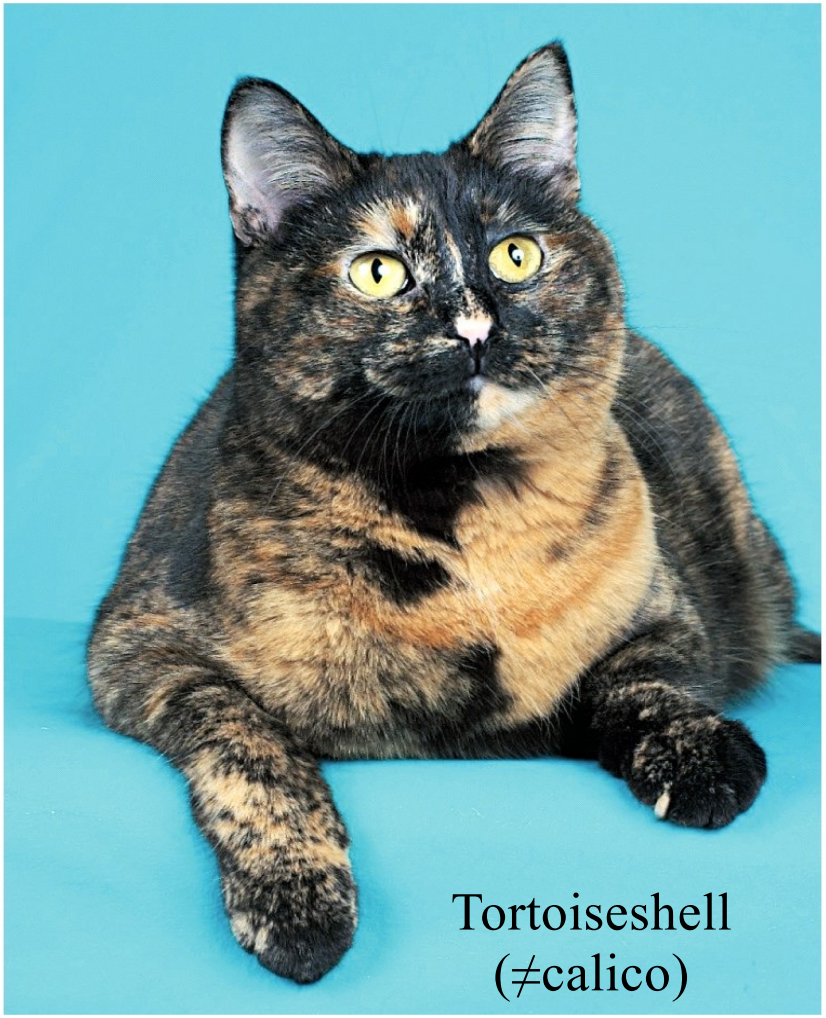
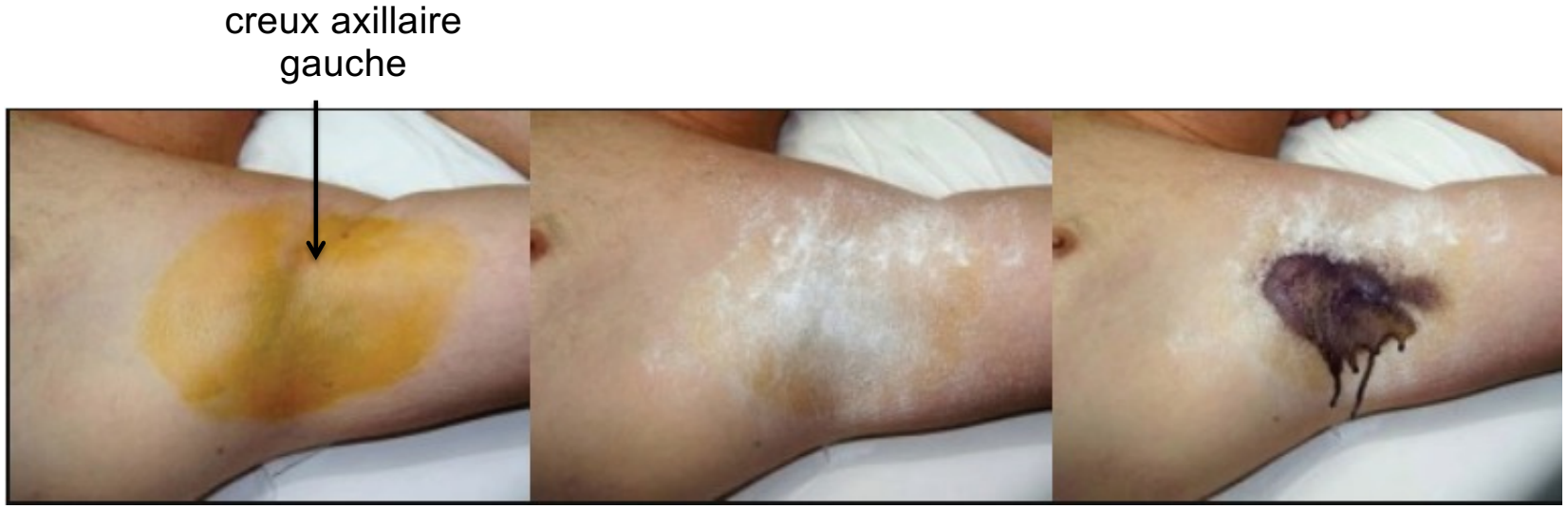


Figure 4-17
Genetics: A Conceptual Approach, Third Edition

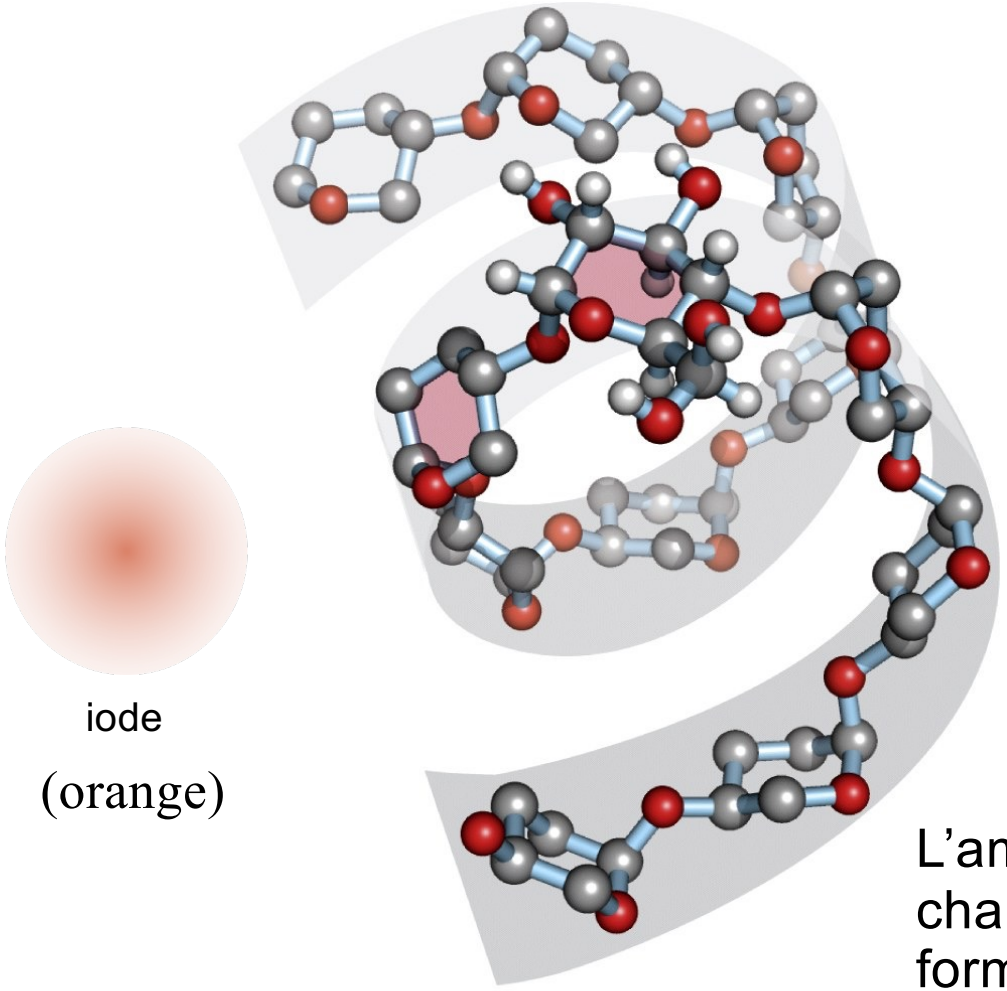
Le test de Minor
(starch iodine test)



1. Une solution iodée est étalée. Laisser sécher
2. De l'amidon (poudre) est saupoudrée sur la région.
3. Transpiration: la sueur permet à l'iode d'interagir avec l'amidon. → couleur foncée

Minor V.
"Ein neues Verfahren zu der klinischen Untersuchung der Schweissabsonderung",
Dtsch Z Nervenheilkd, 1928;101302-7.

A model of a segment of **amylose** :



iode

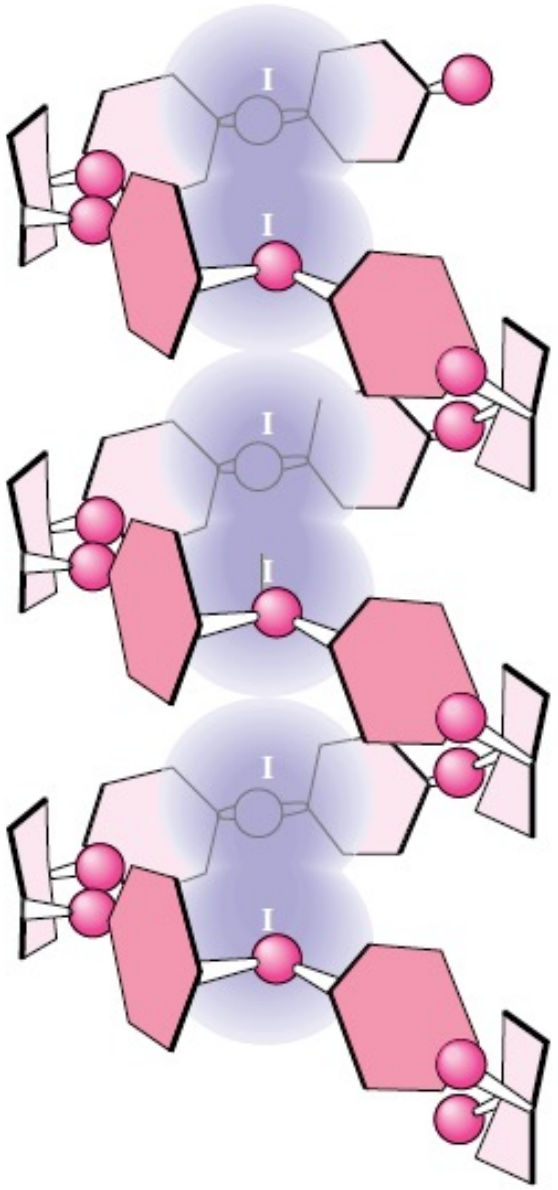
(orange)

L'amylose est une chaine de glucoses formant une hélice.

Figure 7-20b
Lehninger Principles of Biochemistry, Fifth Edition

Amidon :
réaction avec l'iode

FIGURE 7.22 Suspensions of amylose in water adopt a ***helical*** conformation. **Iodine** (I_2) can insert into the middle of the amylose helix to give a **blue color** that is characteristic and diagnostic for starch.



G & G