



FSHD Connect

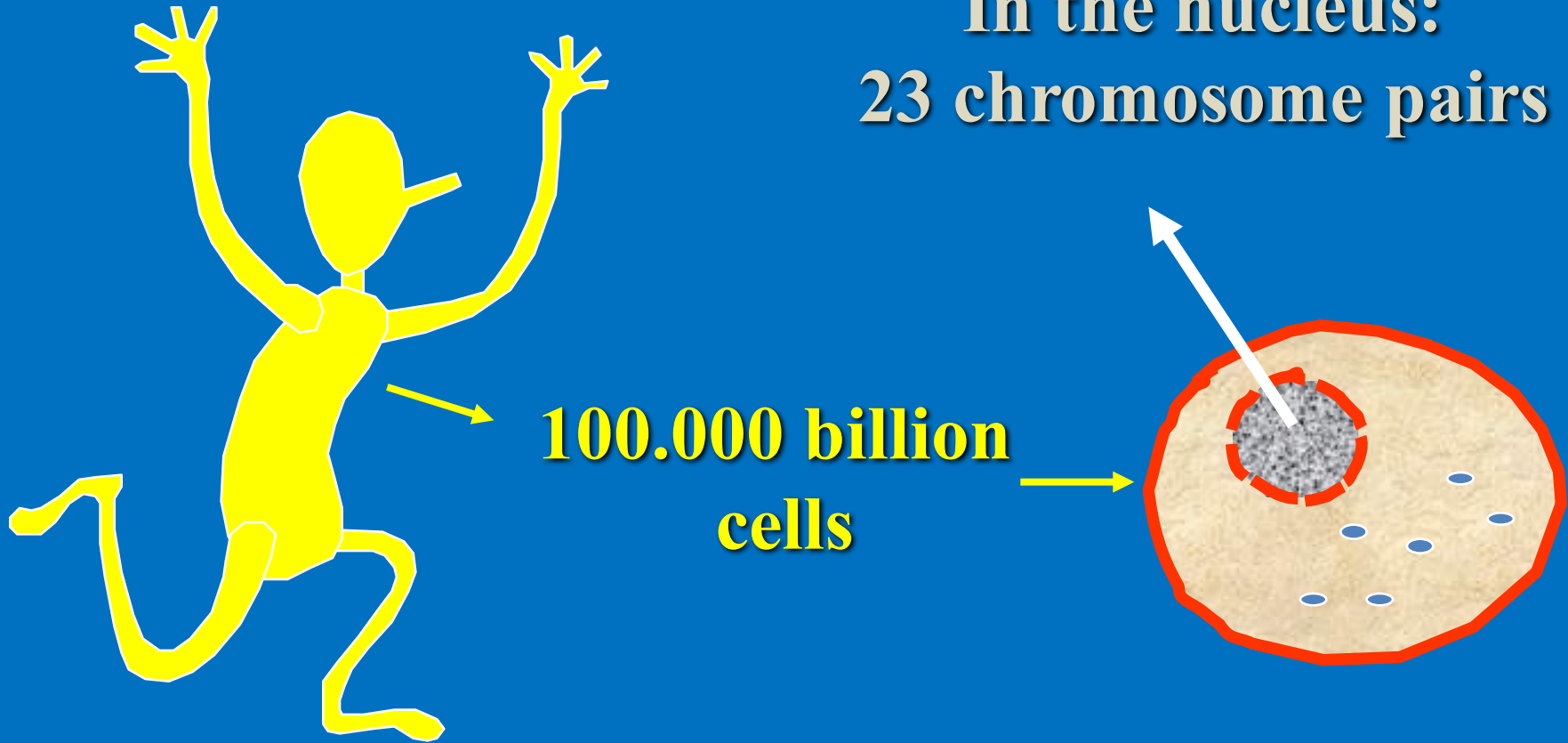


FSHD Science 101

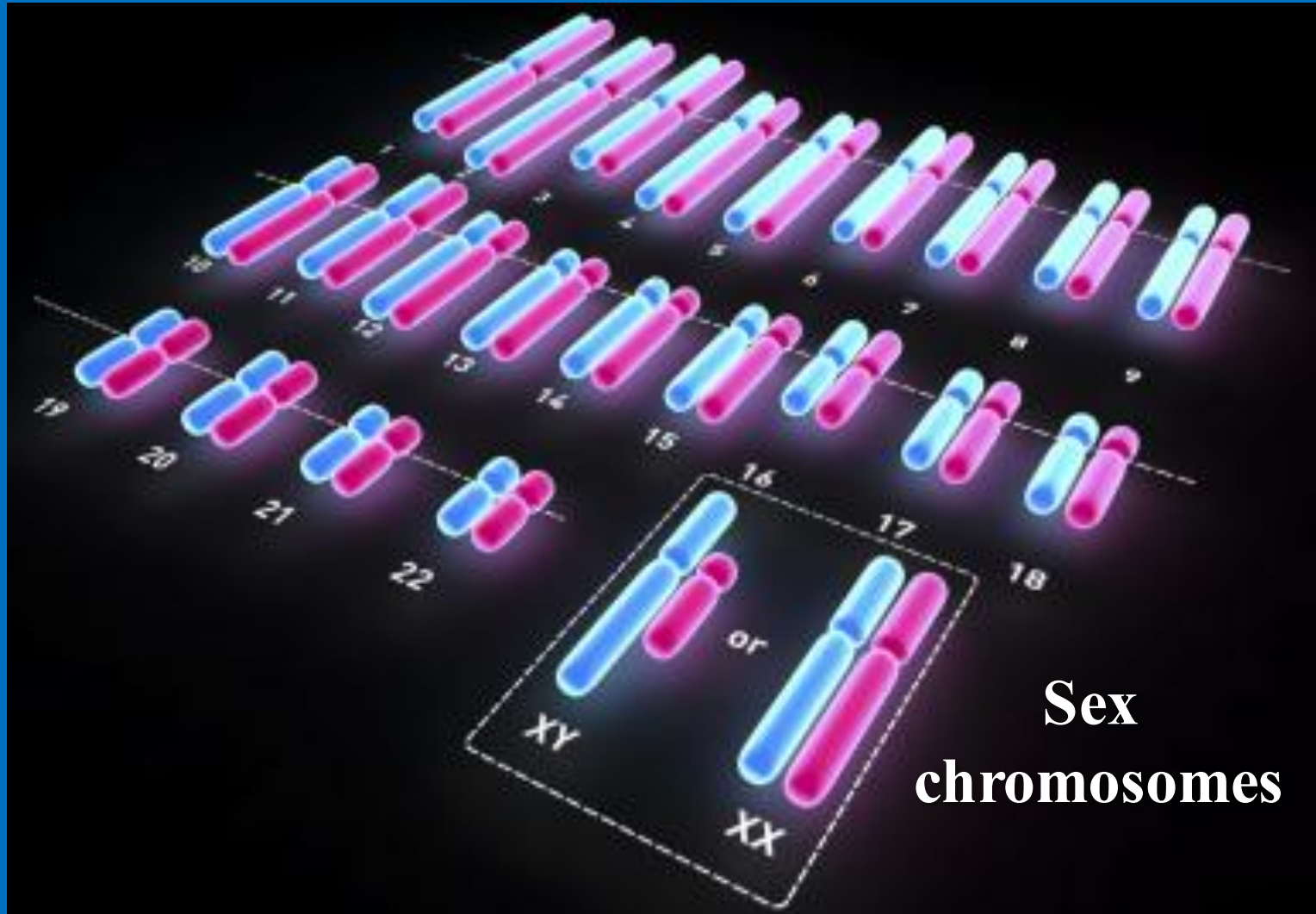
Prof. Alexandra Belayew
University of Mons, Belgium

Every cell of an individual has the same genetic programm

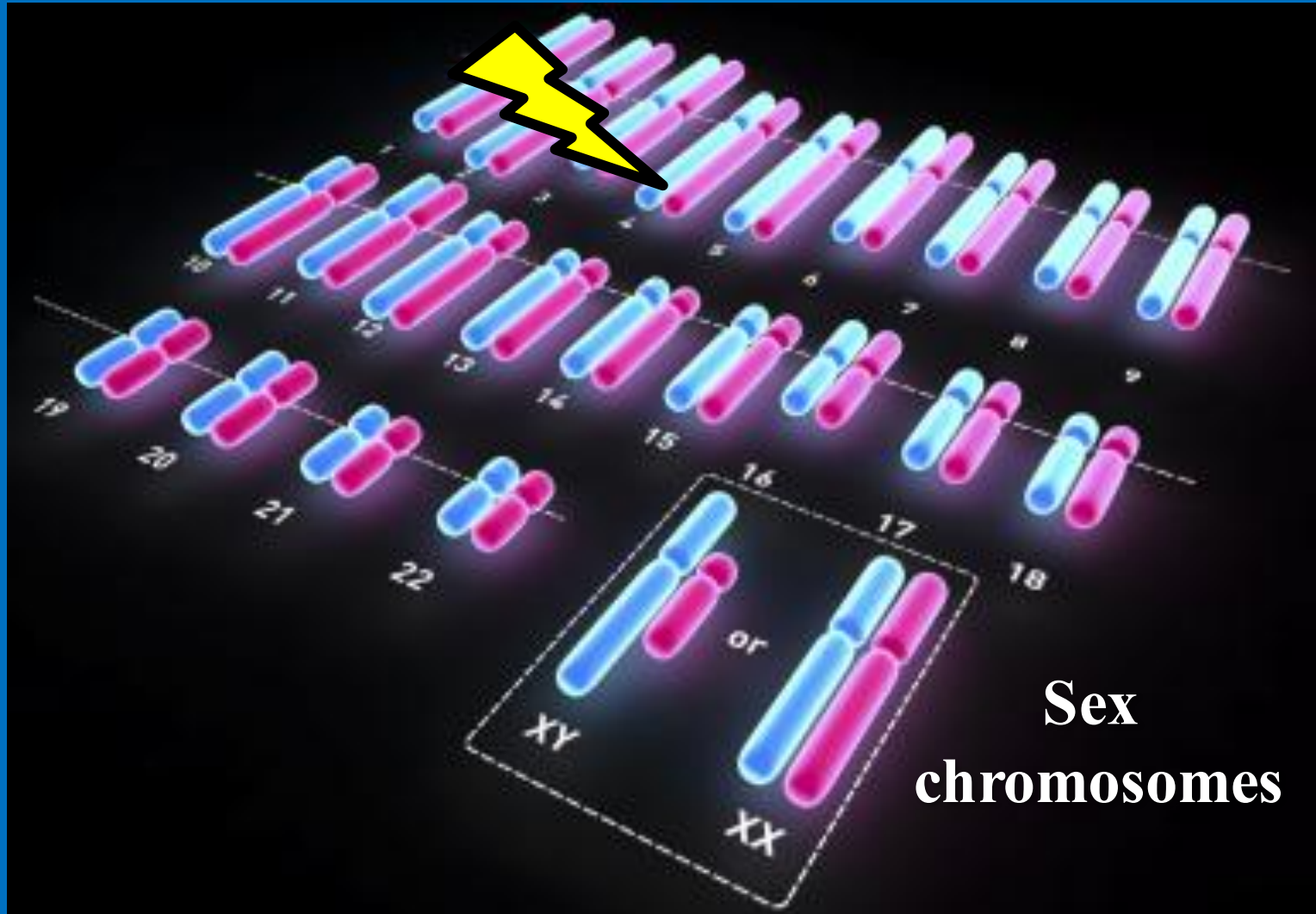
In the nucleus:
23 chromosome pairs



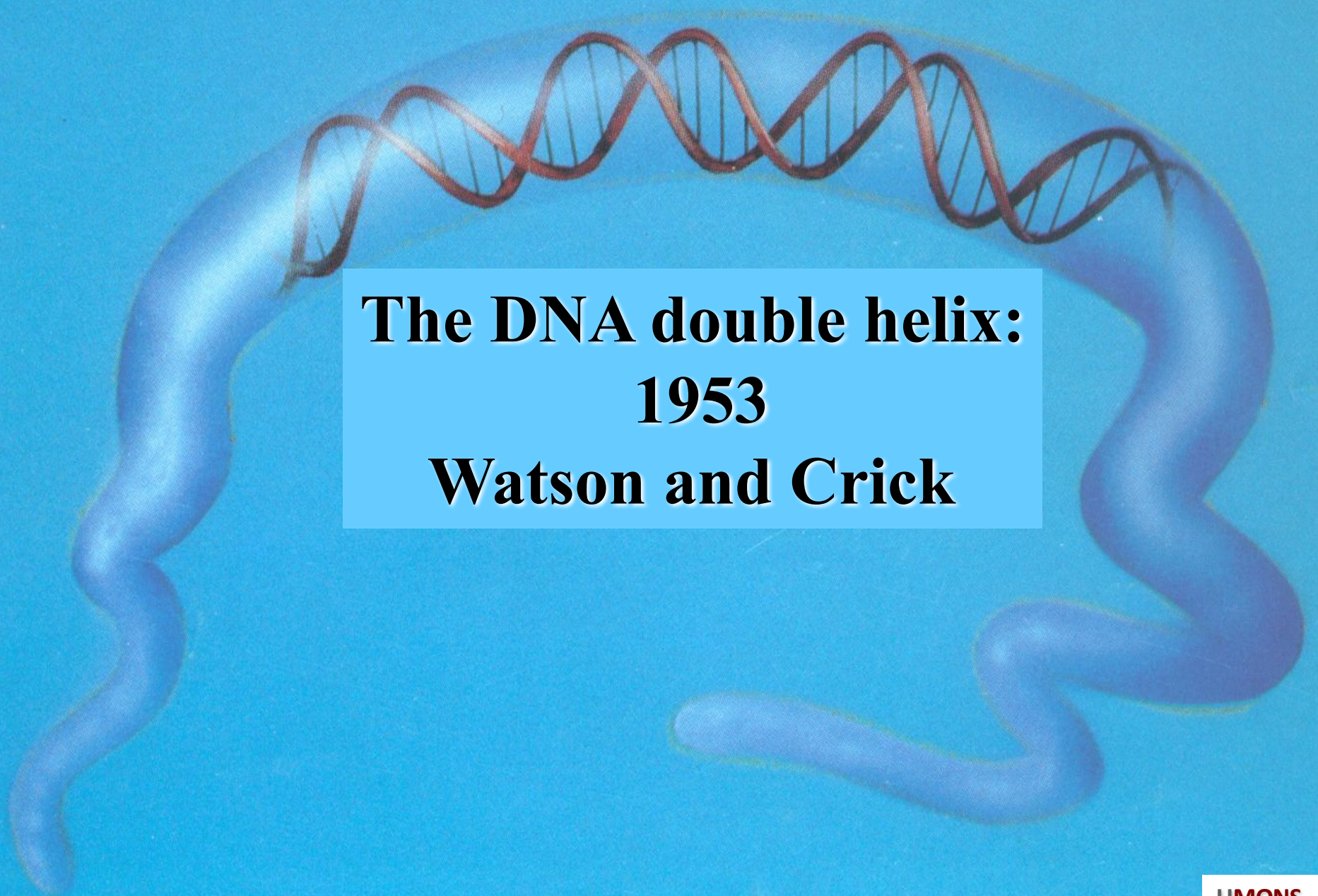
The 23 chromosome pairs : a pair = one chromosome from each parent



The FSHD genetic defect: one chromosome of the chromosome 4 pair

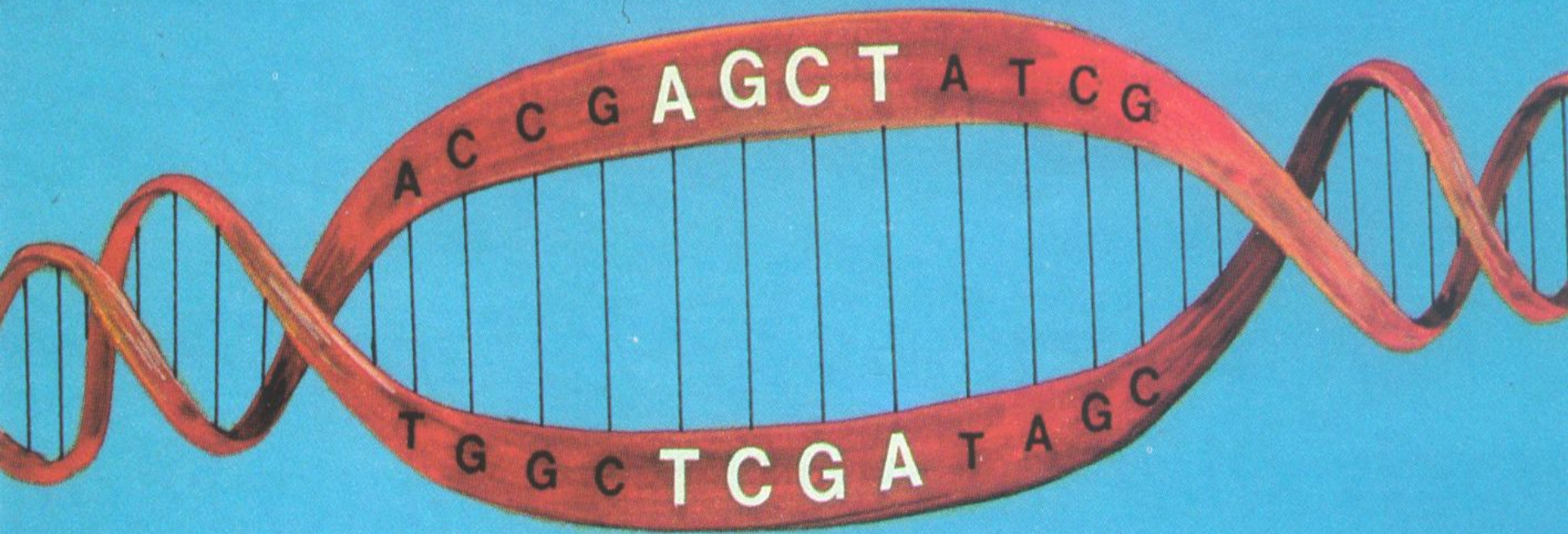


What are chromosomes made of?



**The DNA double helix:
1953
Watson and Crick**

A long chain made with 4 chemicals (letters)...



... forming complementary pairs.

A gene :

**a DNA segment
in which**

**the order of the A, C, G, T letters
states the recipe
to make a protein**

We are made of many different proteins

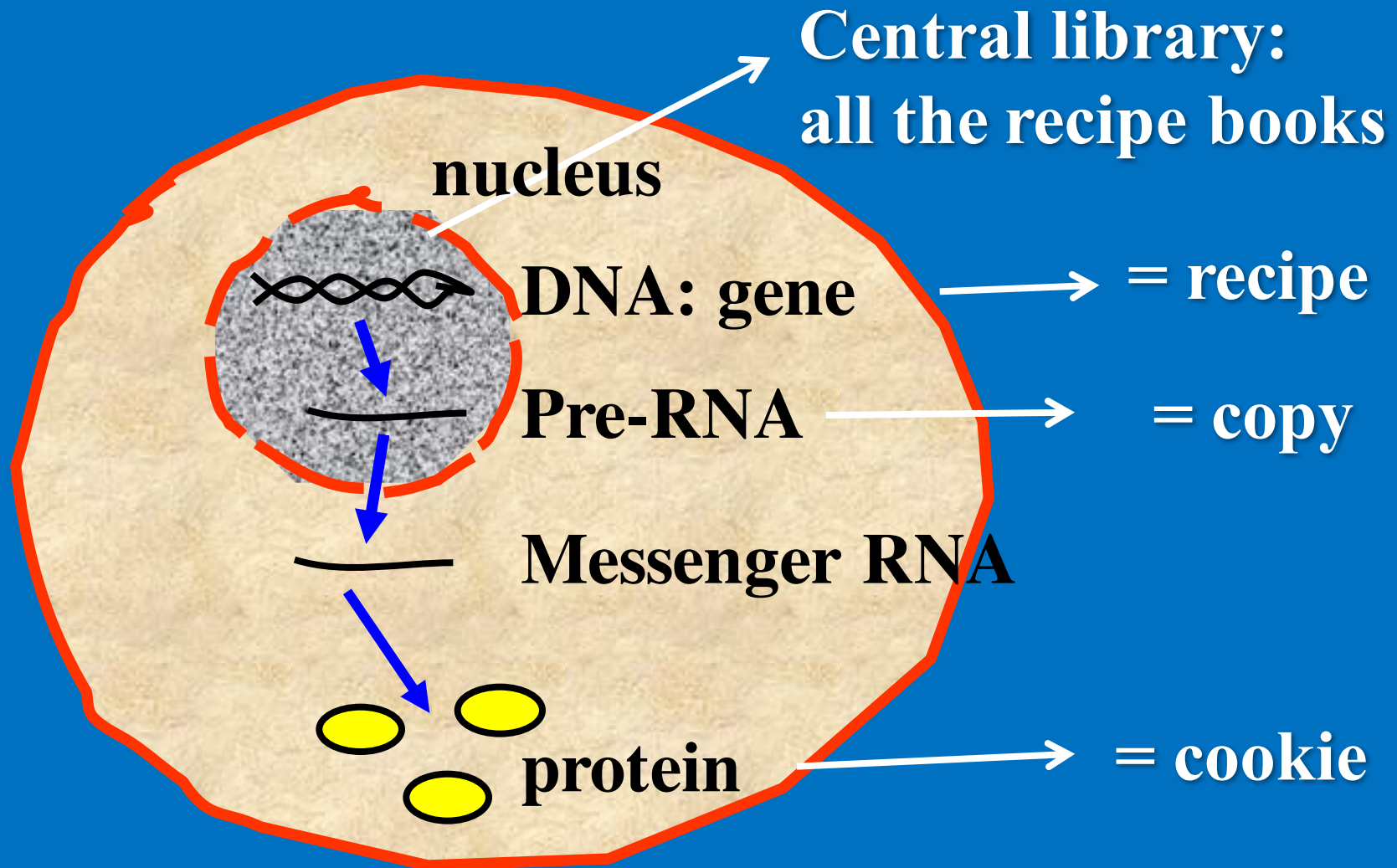


Proteins = cookies!

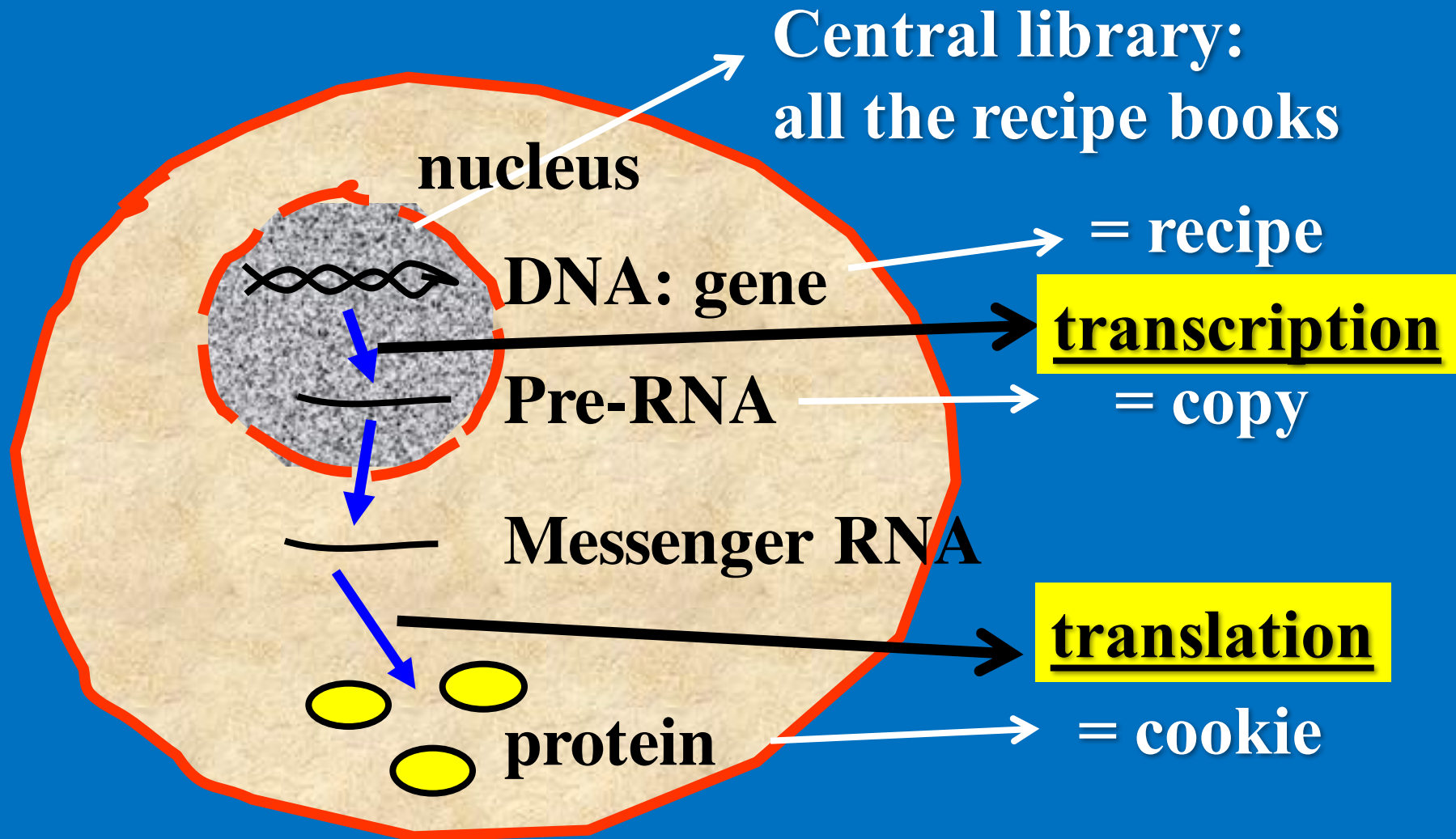


<http://easyday.snydle.com/20-christmas-cookies-to-try-this-holiday-season.html>

Expressing a gene = baking a cookie!



Expressing a gene = baking a cookie!



A cookie



The bakery staff

A cookie Chef!



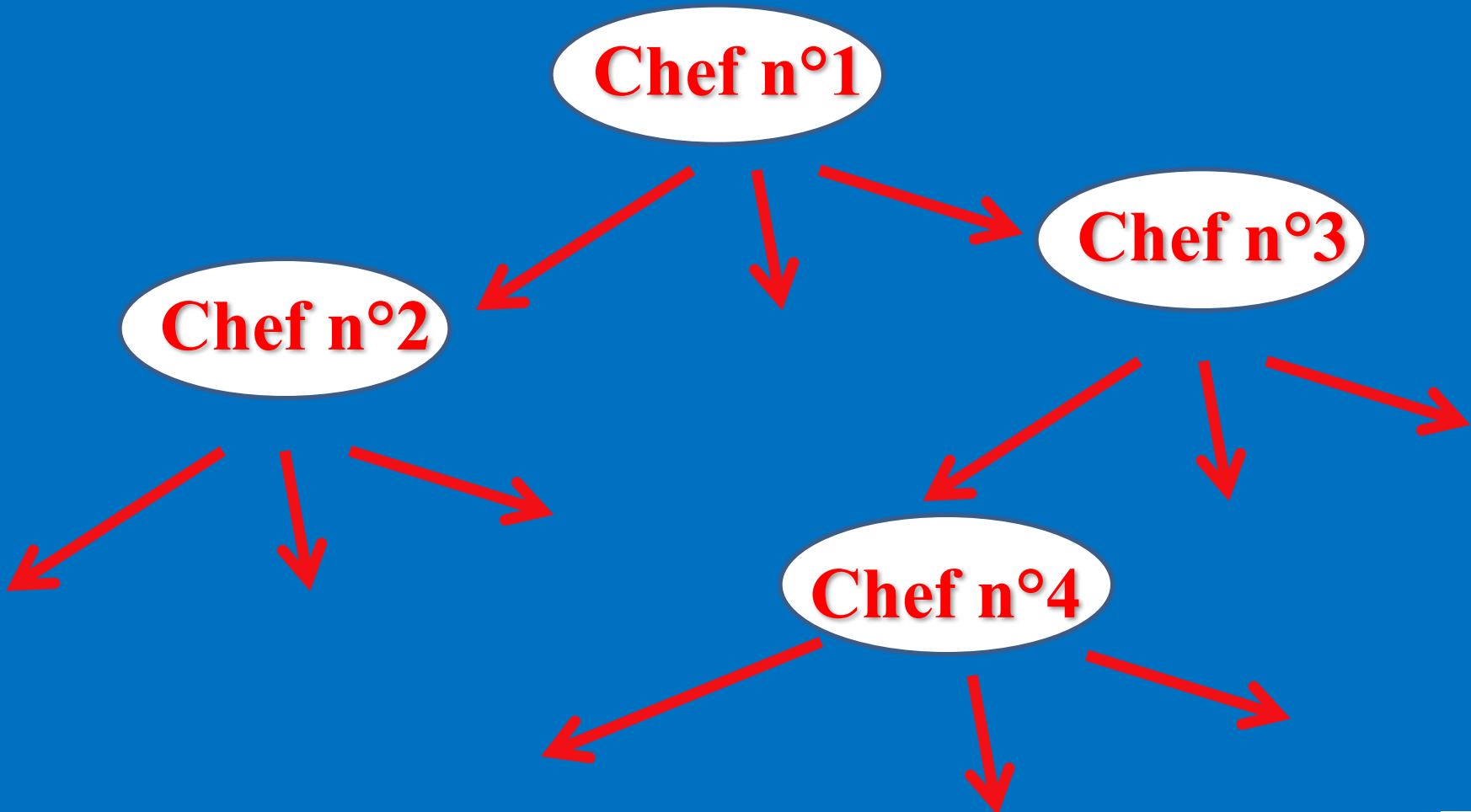
The bakery staff

A cookie Chef!

=> decides
which cookies
get to be baked
in the cell
i.e.
which genes
are switched
on or off

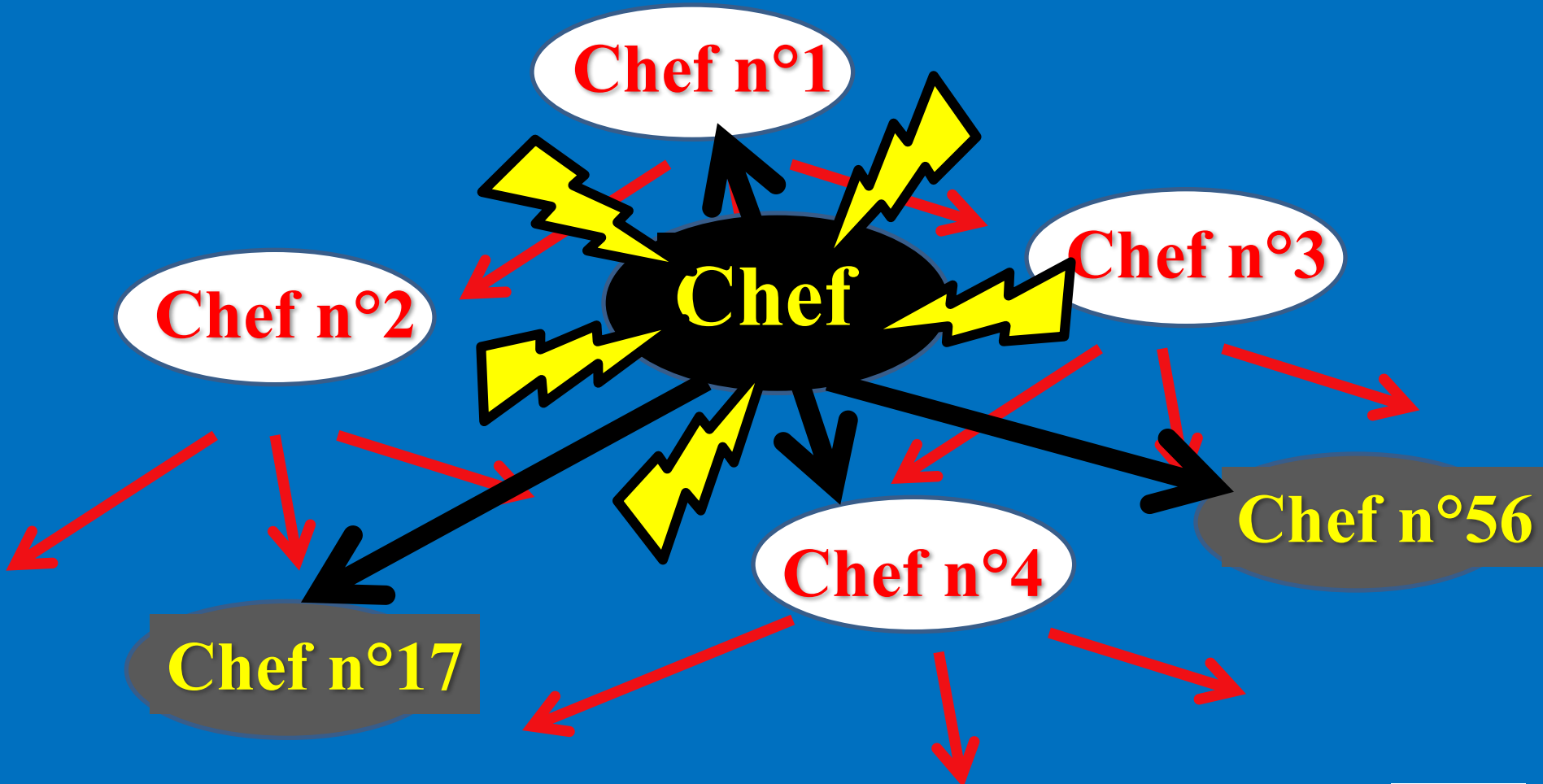


**The bakery staff:
all the cookies that have to bake cookies
need to be organized**



Chaos in the bakery!

The arrival of a crazy Chef

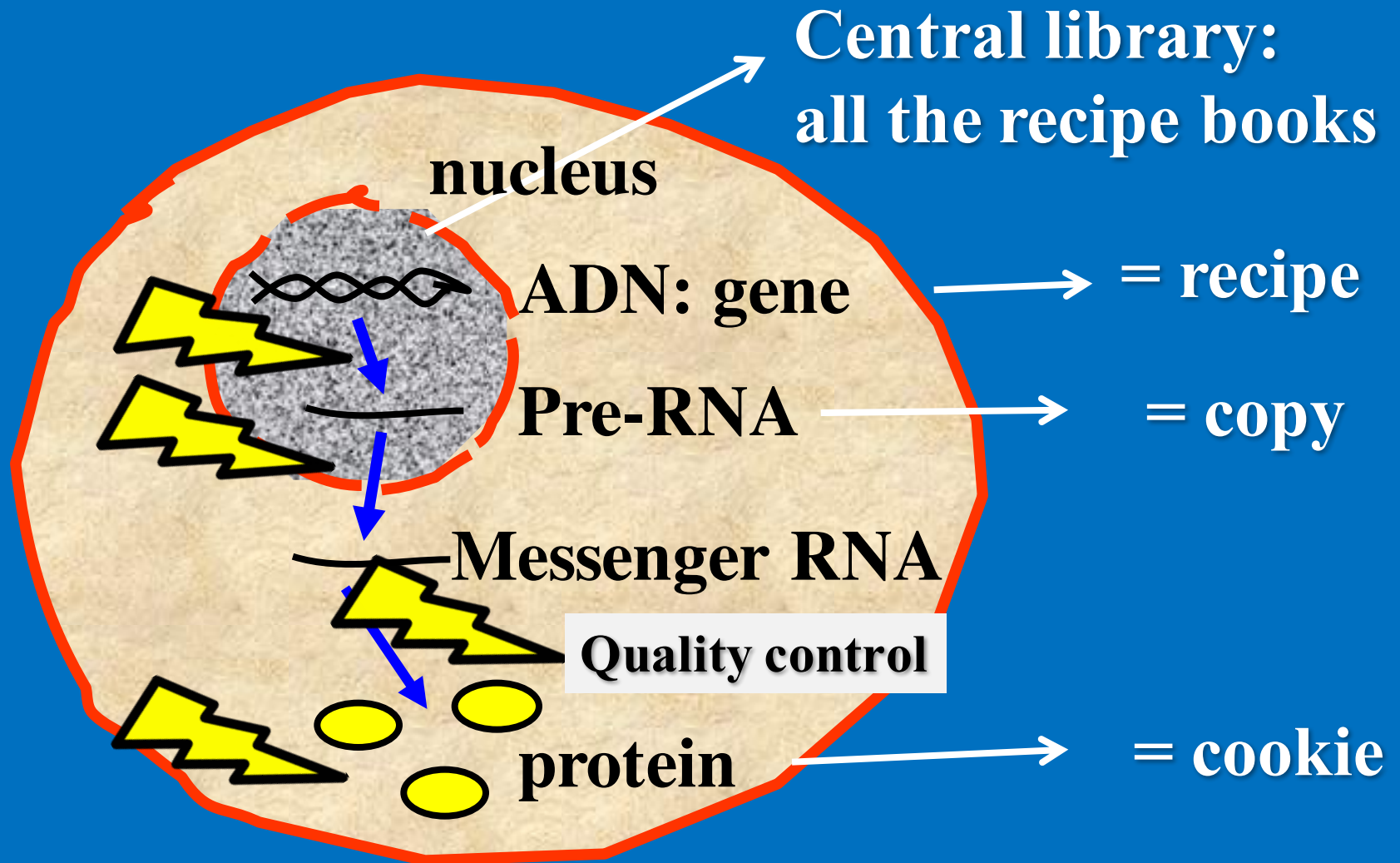


DUX4
is a
crazy
Chef.



It activates
testis genes
in muscles

DUX4 is toxic at all levels in a muscle cell!



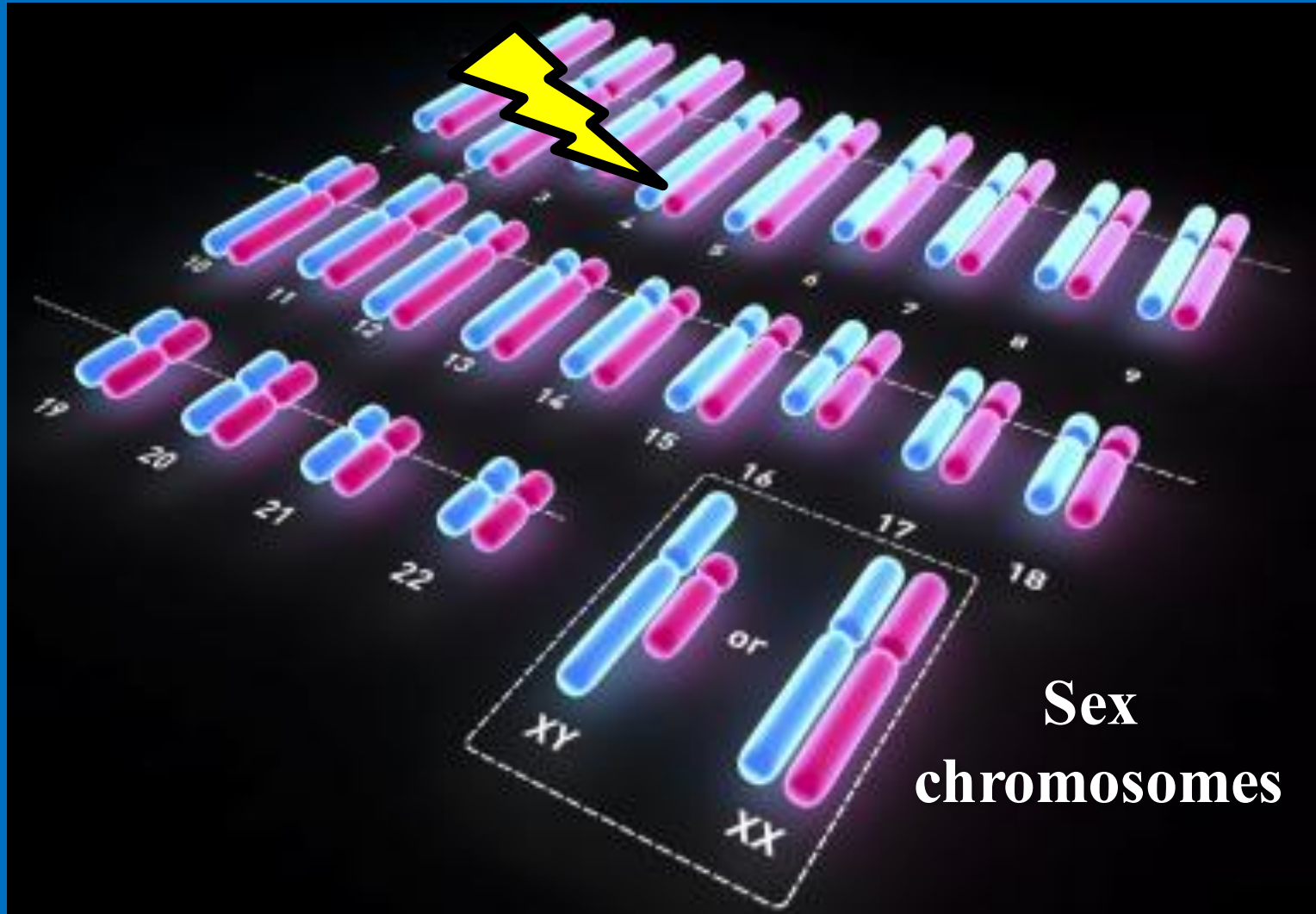
Conditions to develop FSHD

1) Genetic condition:

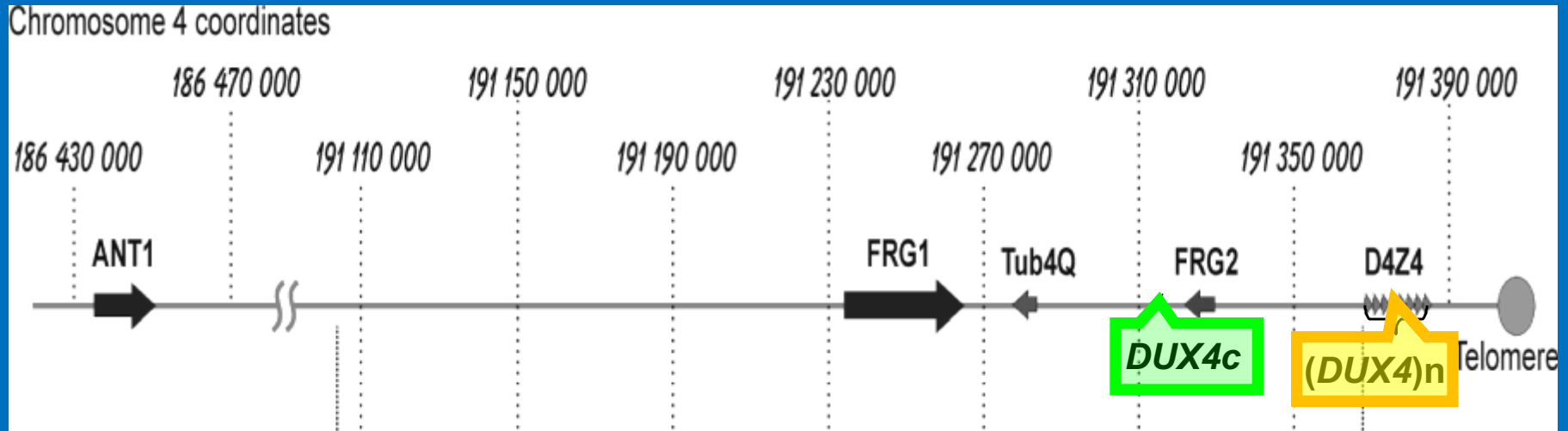
DUX4 gene with an end

=> toxic protein

The FSHD genetic defect: one chromosome of the chromosome 4 pair



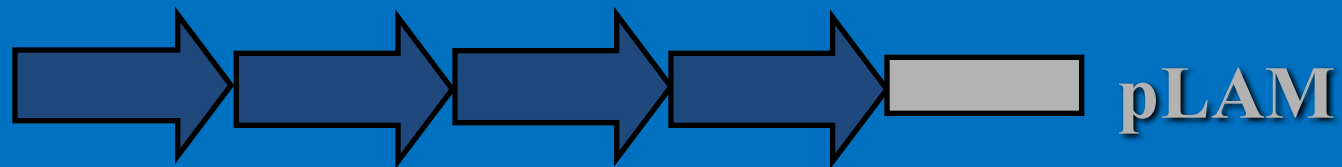
The FSHD locus in 4q35.



DoUble homeoboX
genes

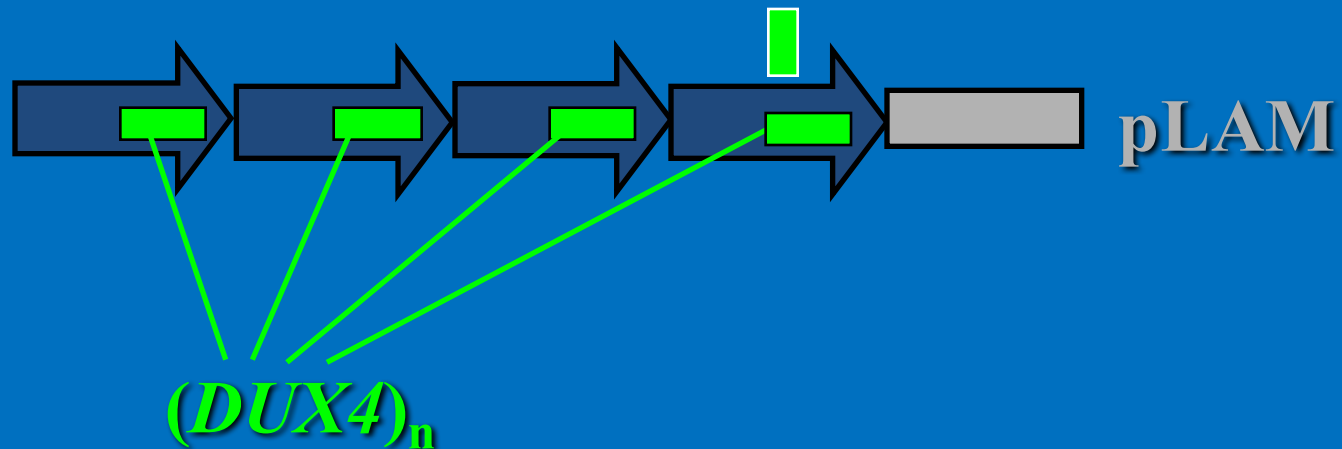


The D4Z4 repeated elements: decrease in copy number is linked to FSHD1



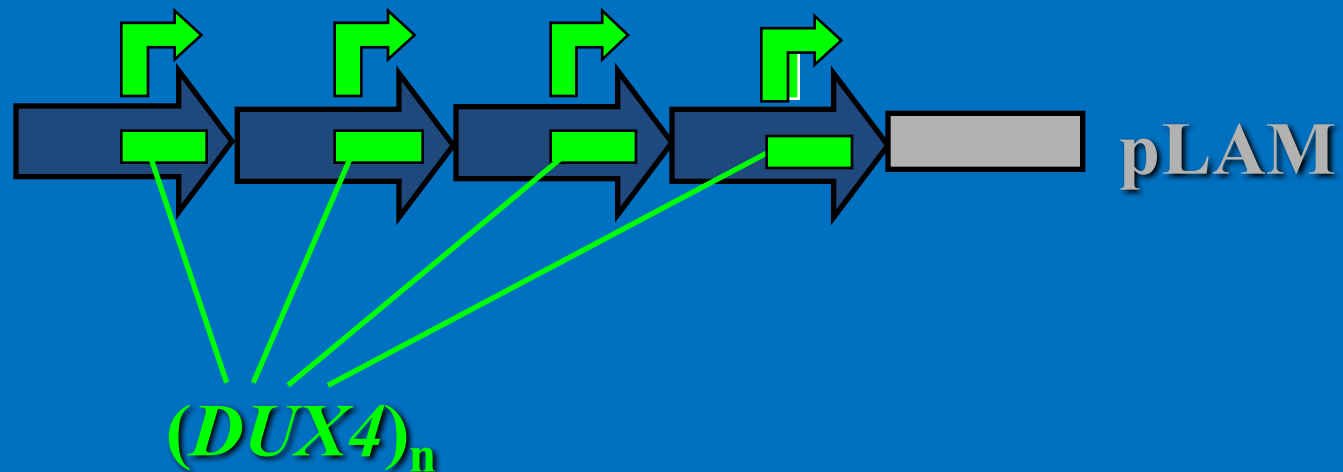
Van Deutekon et al, 1993; Wijmenga et al, 1994

Each D4Z4 unit contains a recipe with a double homeobox



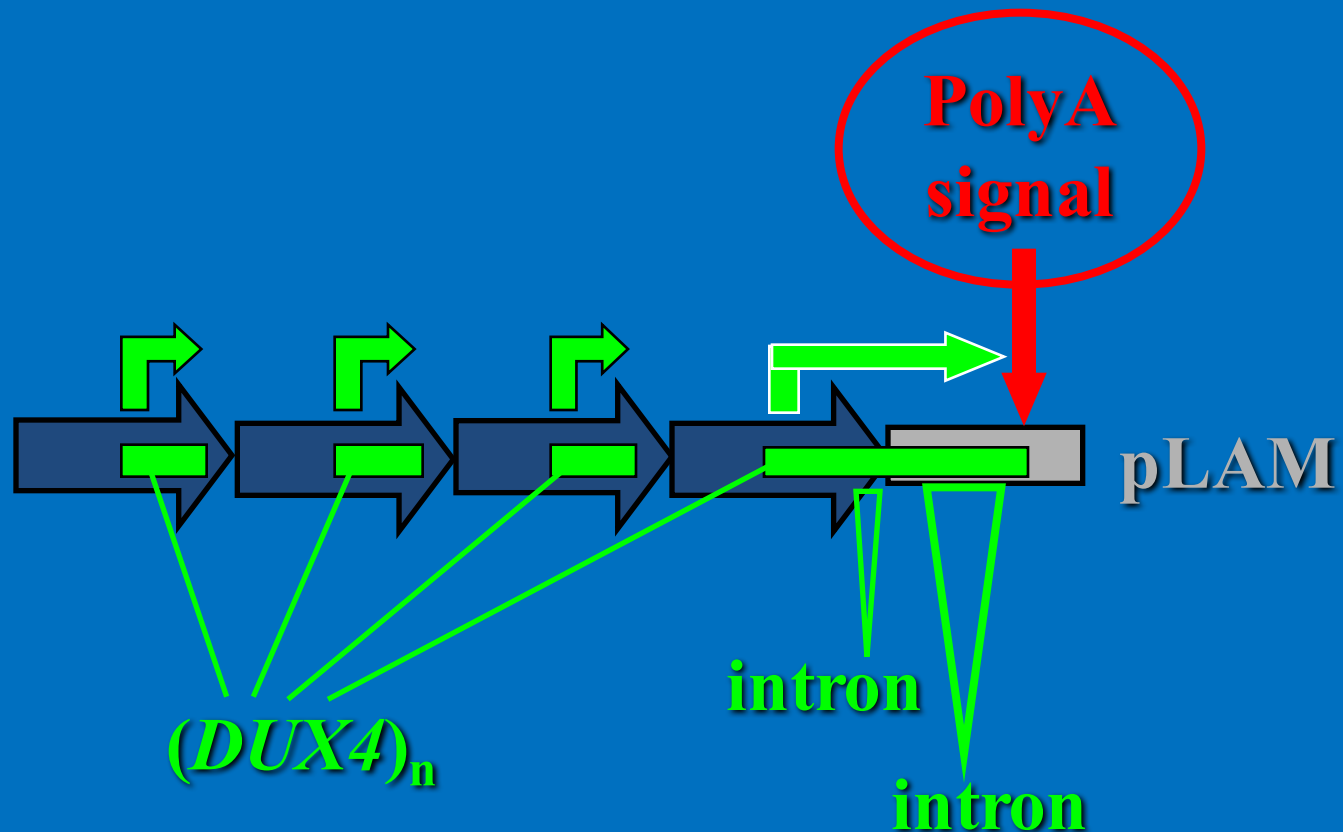
Hewitt et al, 1994

Each D4Z4 unit contains a DUX4 gene



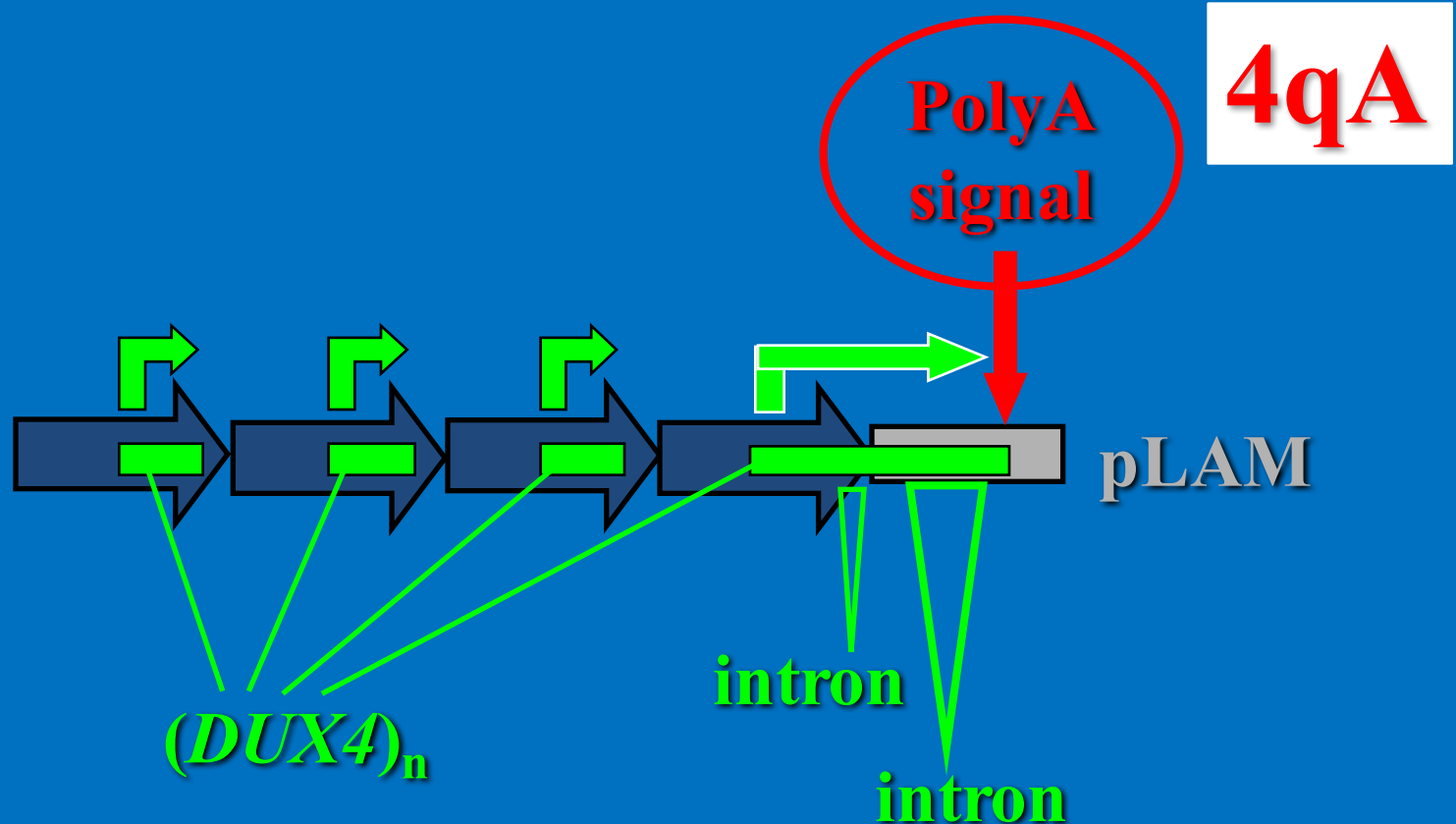
Gabriels et al, 1999; Kowaljow et al, 2007

Only the last DUX4 gene has an end!



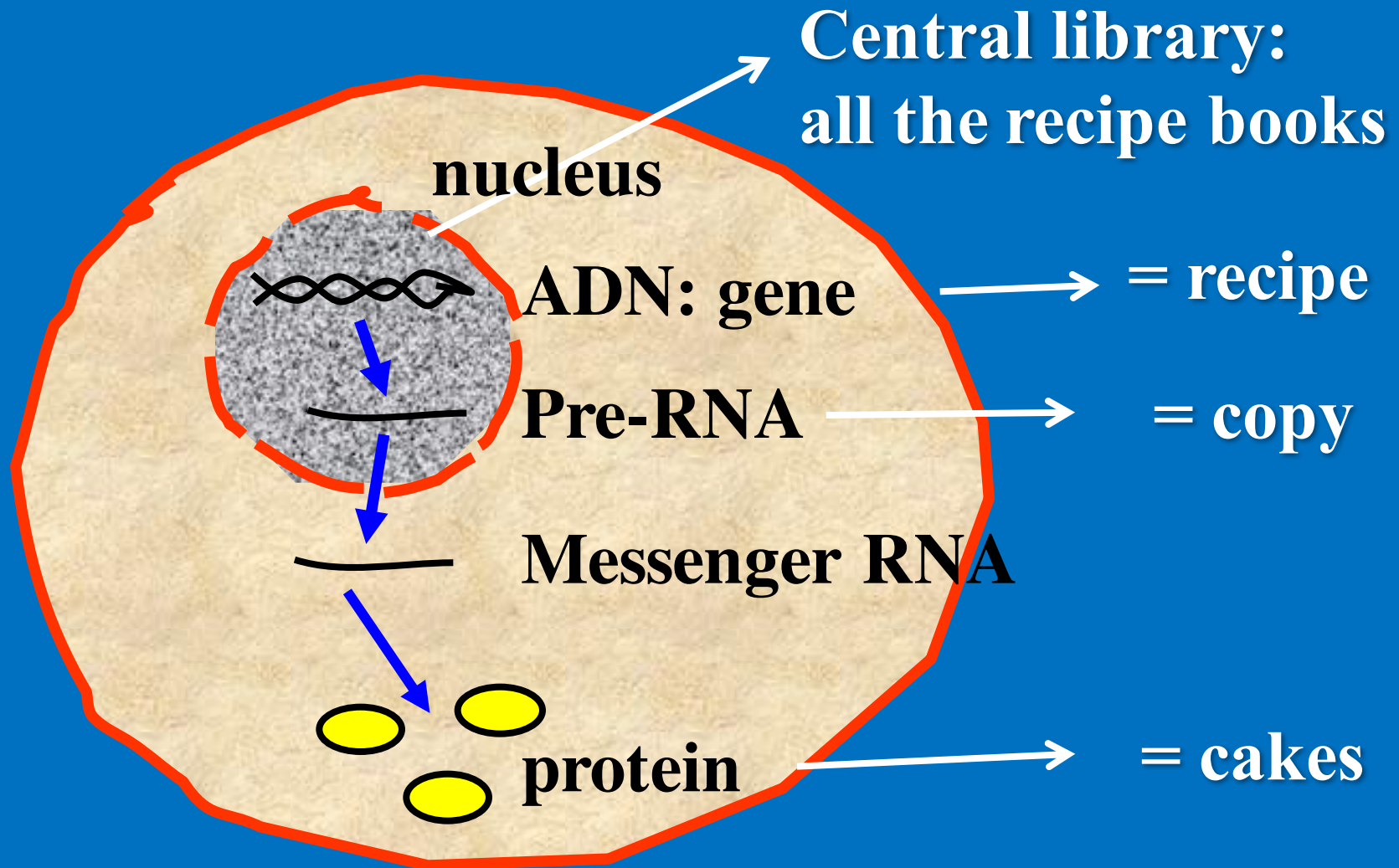
Dixit *et al.* 2007, Lemmers *et al.* 2011

Only the last DUX4 gene has an end!

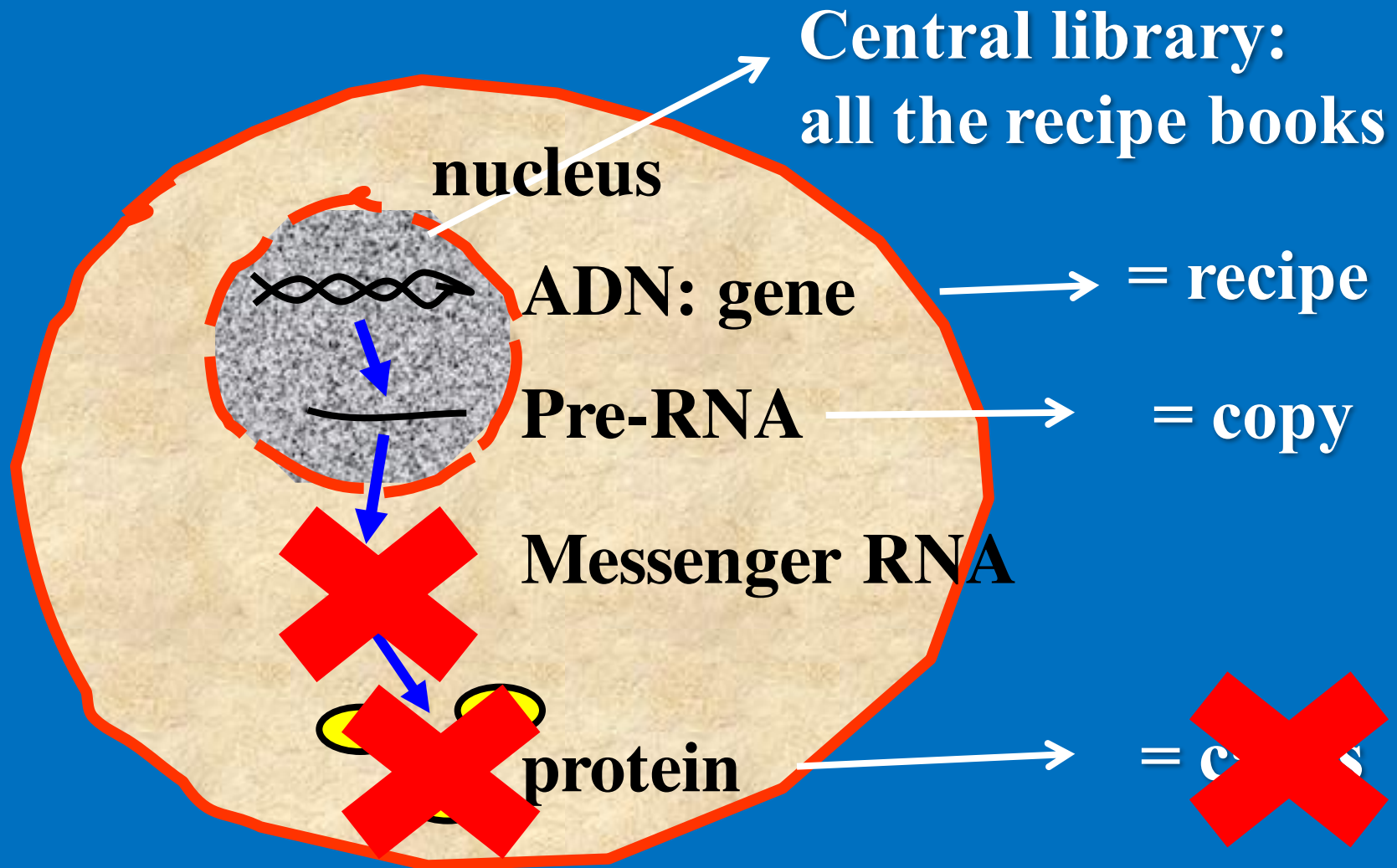


Dixit *et al.* 2007, Lemmers *et al.* 2011

4qA allele => DUX4 protein expression



4qB allele => no DUX4 protein expression



Conditions to develop FSHD

1) Genetic condition:

DUX4 gene with an end

=> toxic protein

Conditions to develop FSHD

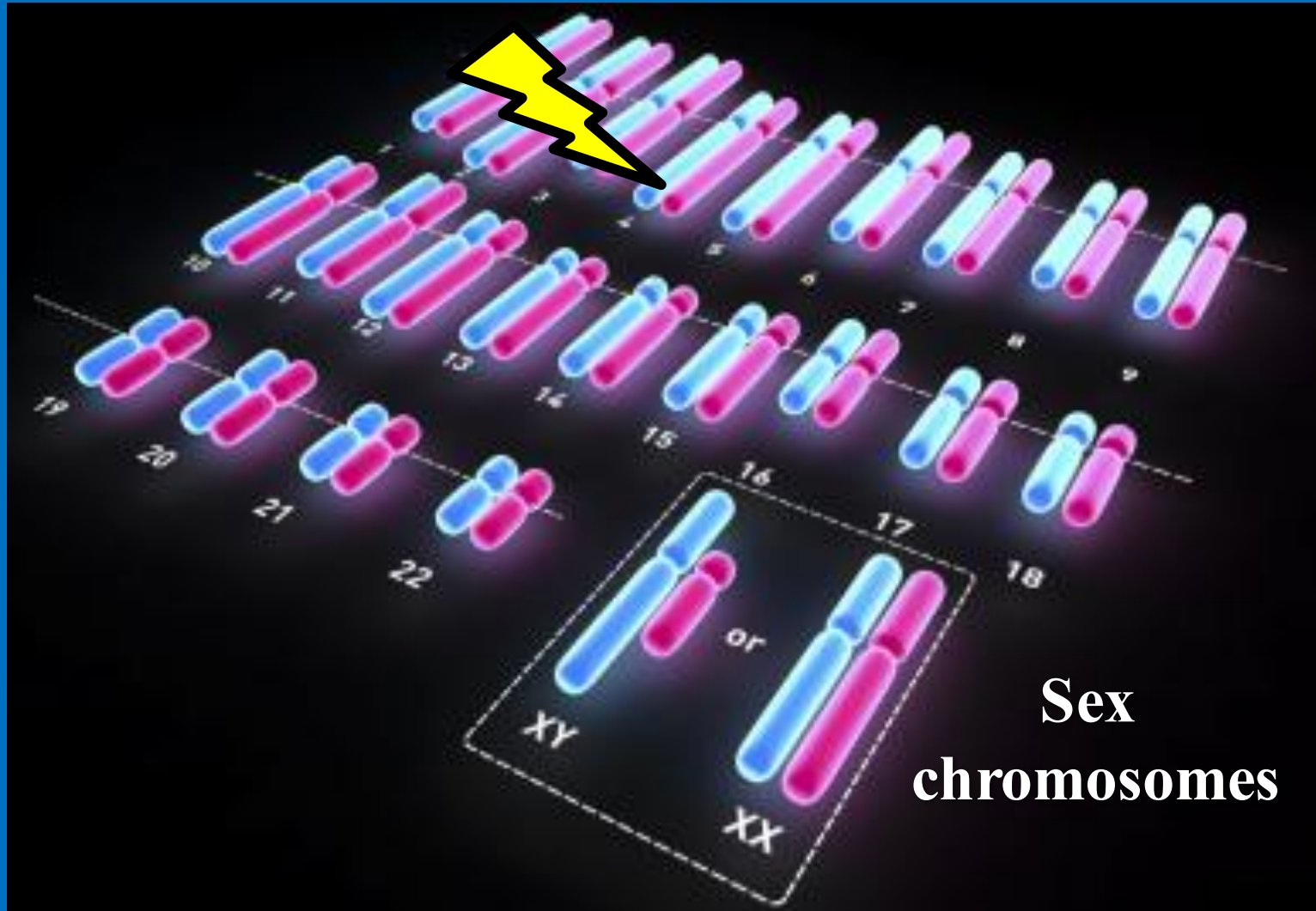
1) Genetic condition:

DUX4 gene with an end (PAS)
stable messenger RNA
toxic protein

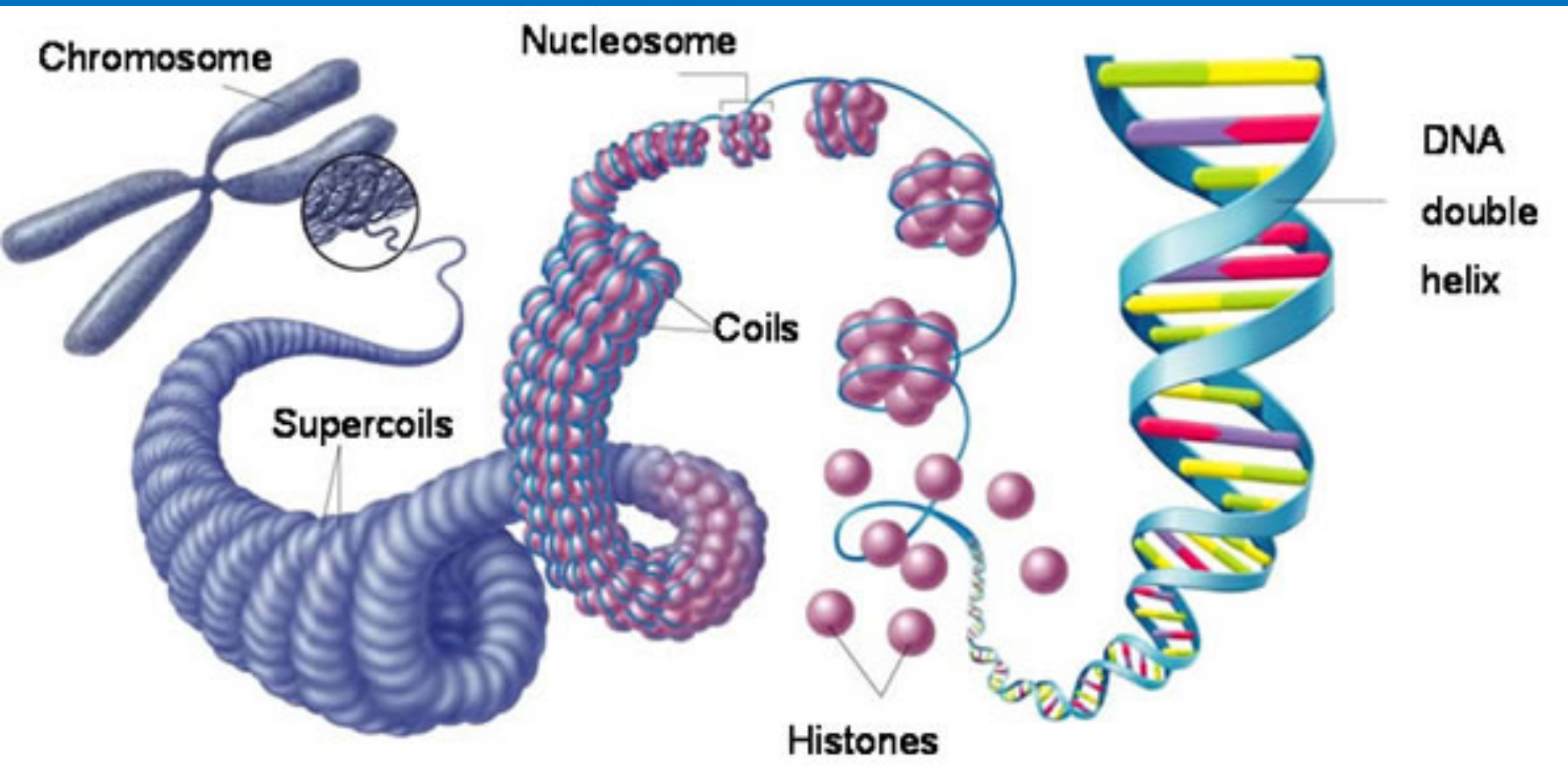
2) Epigenetic condition:

DUX4 gene in open chromatin

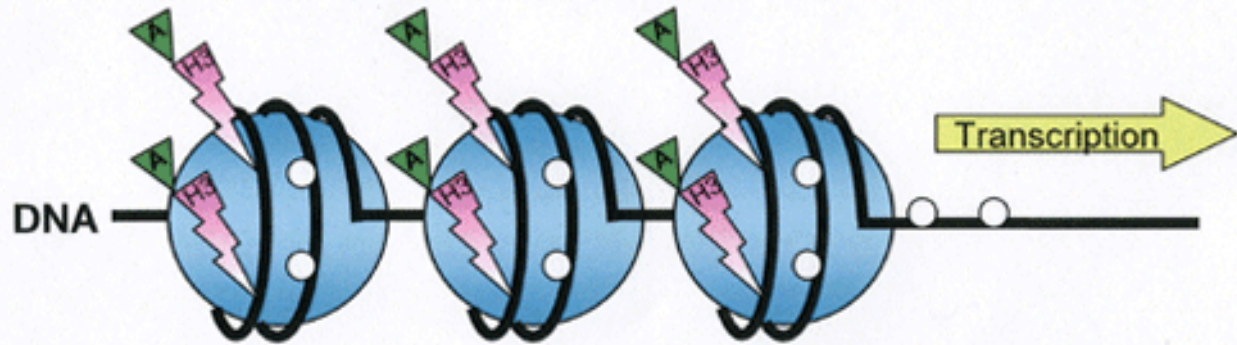
The FSHD genetic defect: one chromosome of the chromosome 4 pair



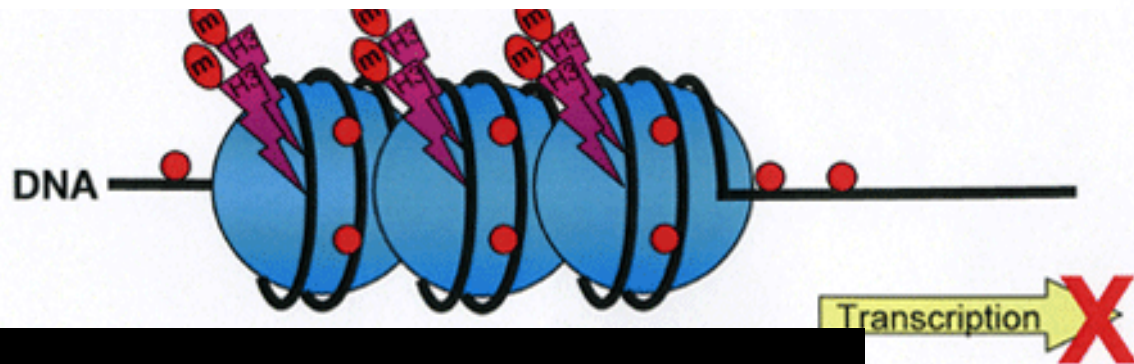
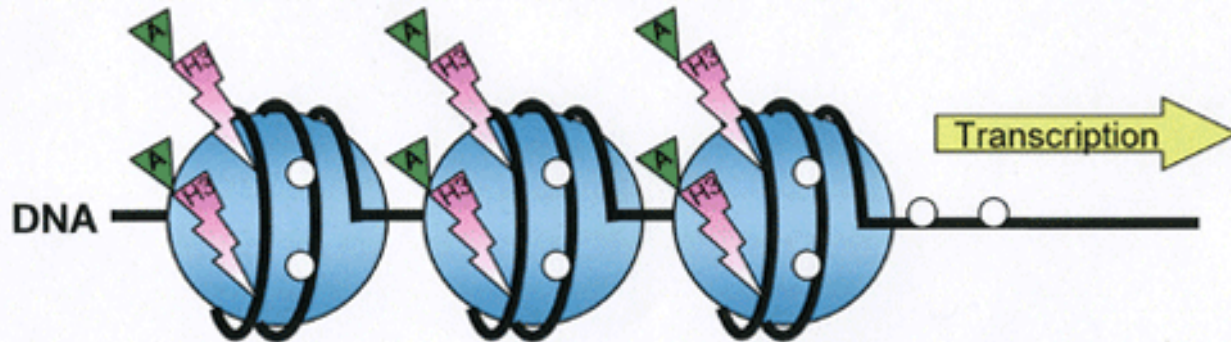
In chromosomes DNA is packed up with proteins = chromatin



Open, active chromatin

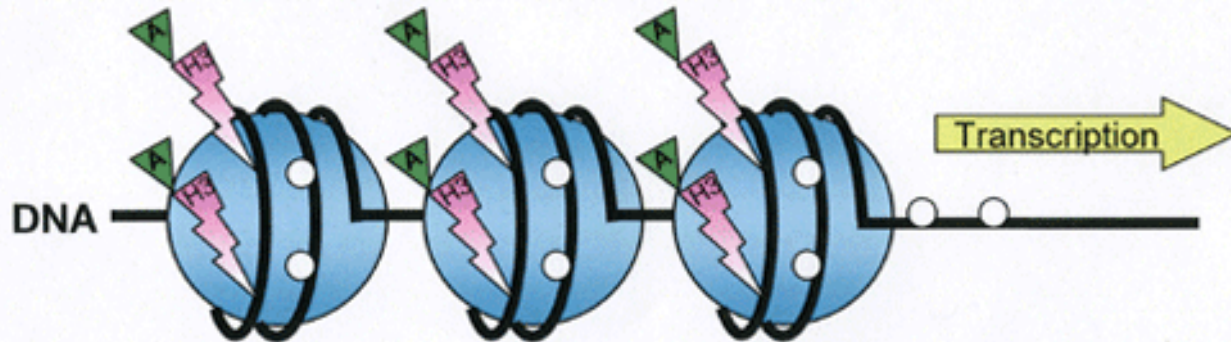


Open, active chromatin

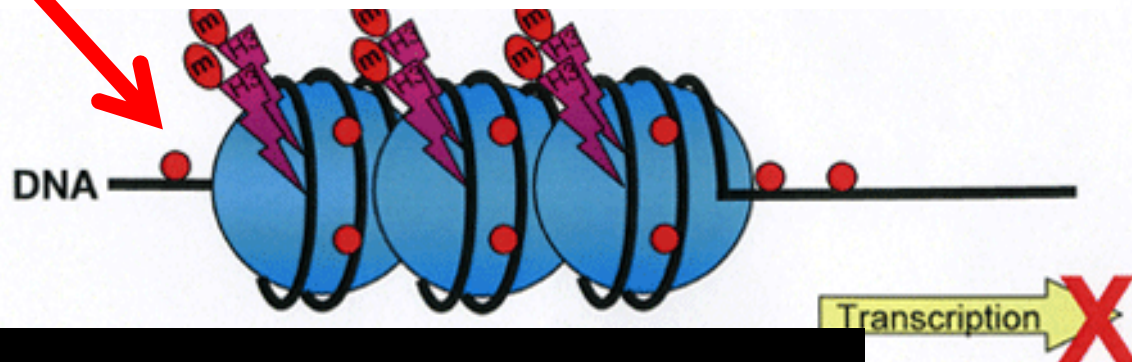


Compact, inactive chromatin

Open, active chromatin

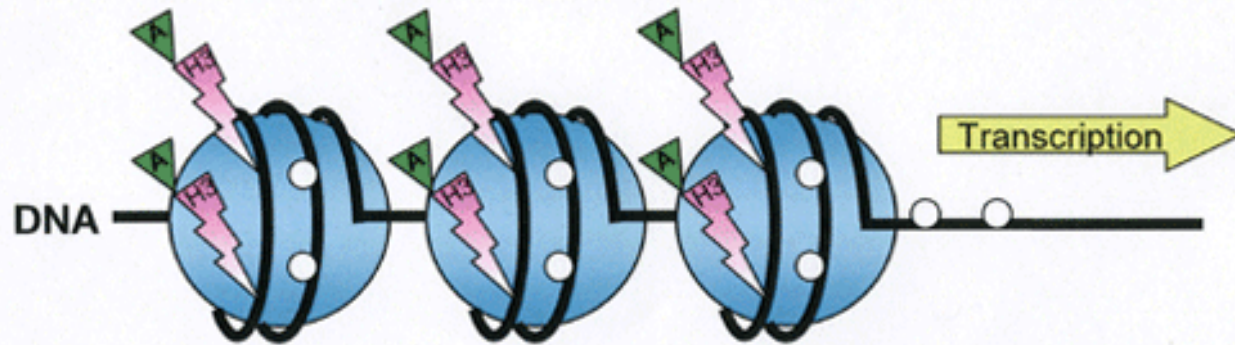


DNA methylation: $C \Rightarrow \overset{\bullet}{C}$

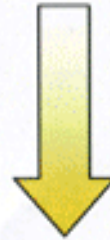


Compact, inactive chromatin

Open, active chromatin



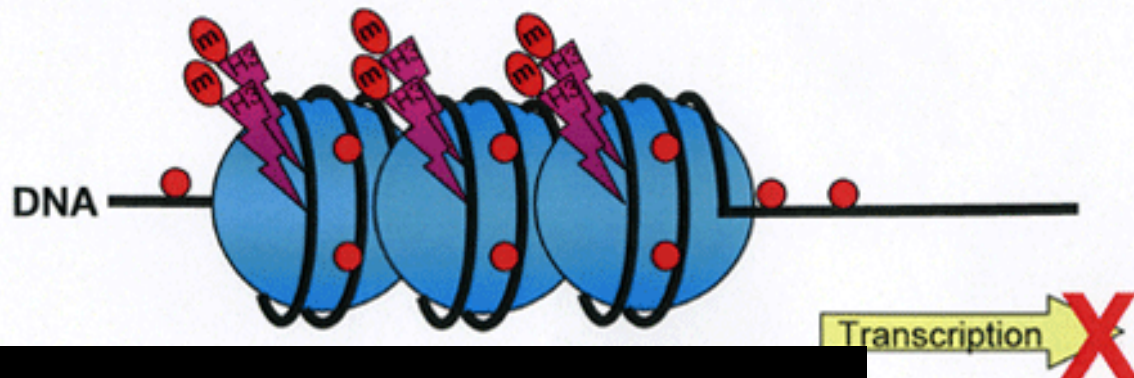
**Enzymes
open or
pack up
chromatin**



SMCHD1

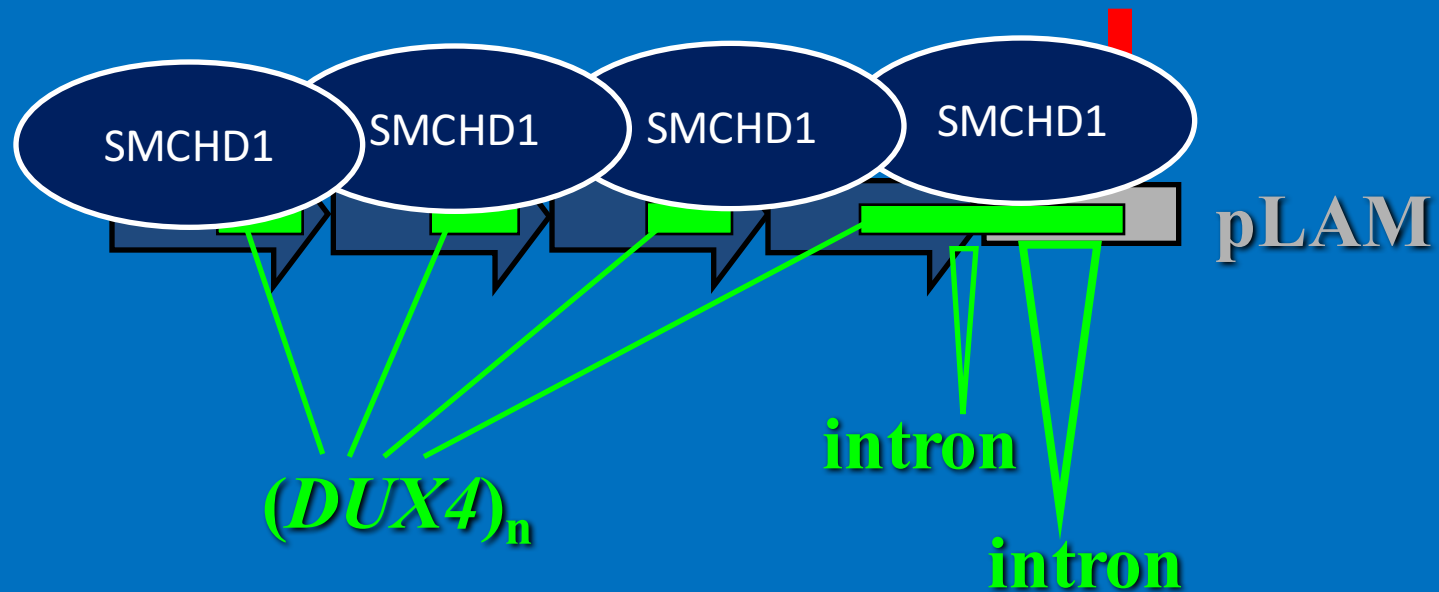
+ MBPs

DNMT3B

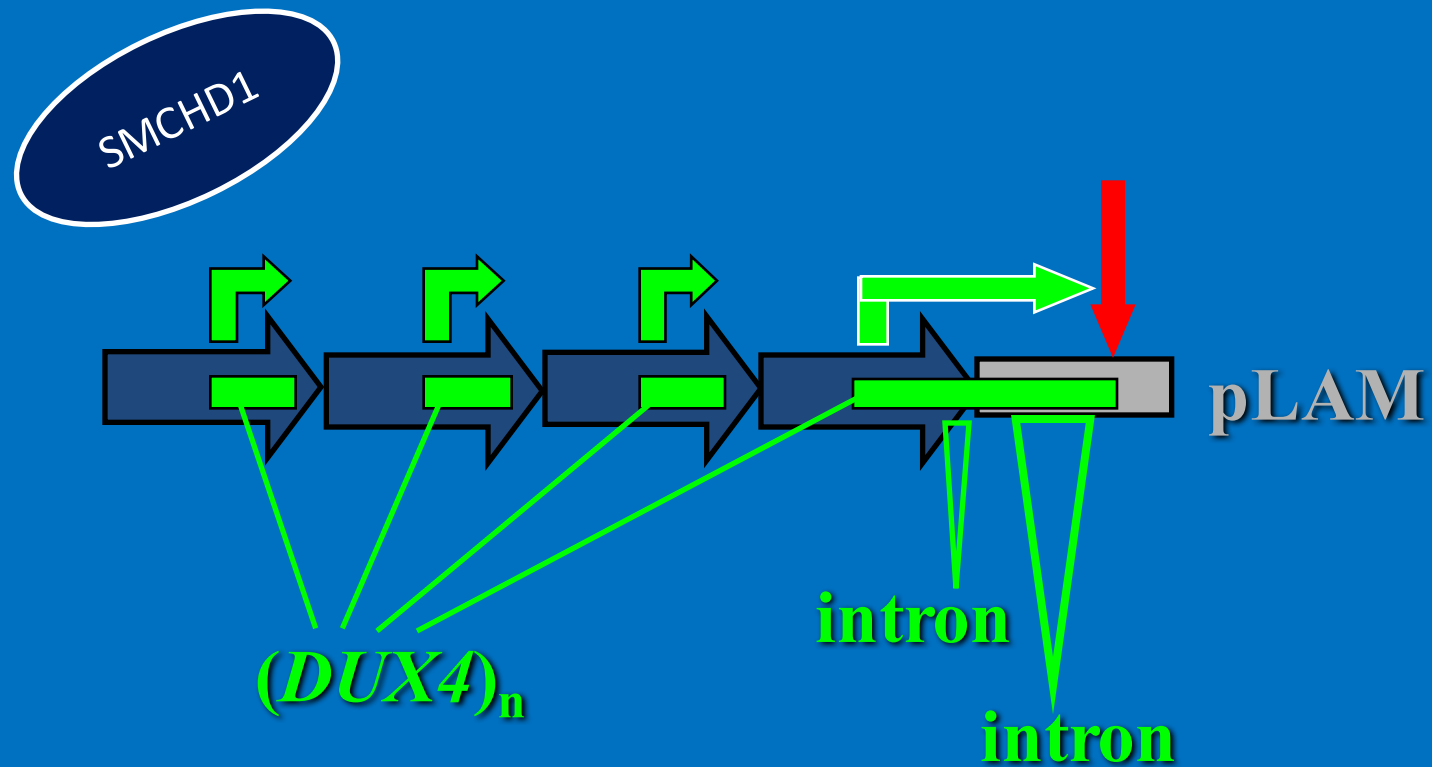


Compact, inactive chromatin

**The DUX4 gene is normally « hidden »:
methylated DNA, inactive chromatin
=> no RNA, no DUX4 protein made, no FSHD**



FSHD: *DUX4* gene is not « hidden »
DNA has a low methylation,
chromatin is open, *DUX4* protein is made



Conditions for FSHD development

1) Genetic condition:

DUX4 gene with polyA addition signal (PAS)

=> stable mRNA => toxic protein

2) Epigenetic condition:

DNA hypomethylation

open chromatin

DUX4 gene transcription

- FSHD1: *D4Z4* copy number = 1-10
- FSHD2: *SMCHD1* (chr 18) loss of function
DNMT3B (chr 20) loss of function

DUX4
is a
crazy
Chef
and a
muscle
killer

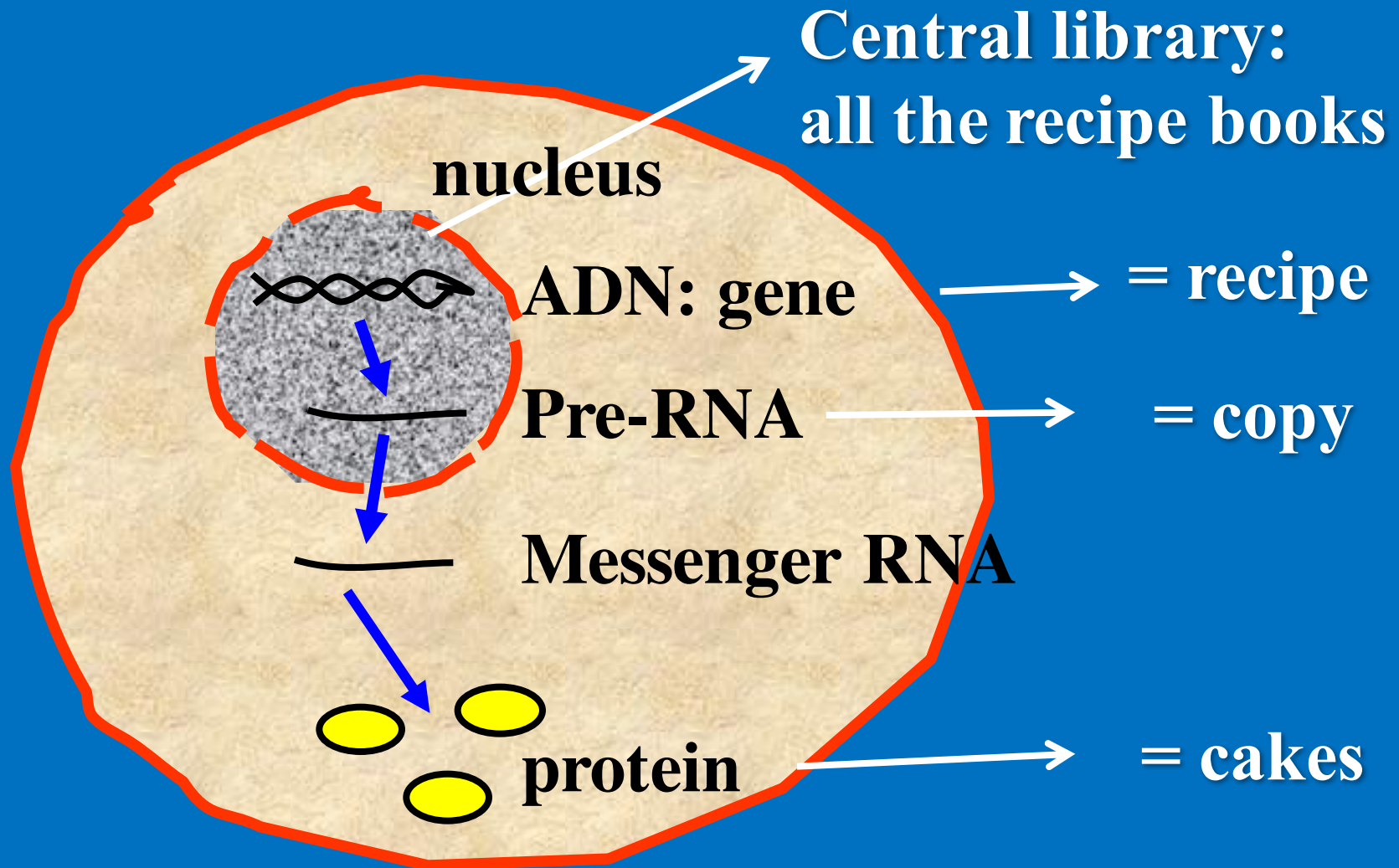


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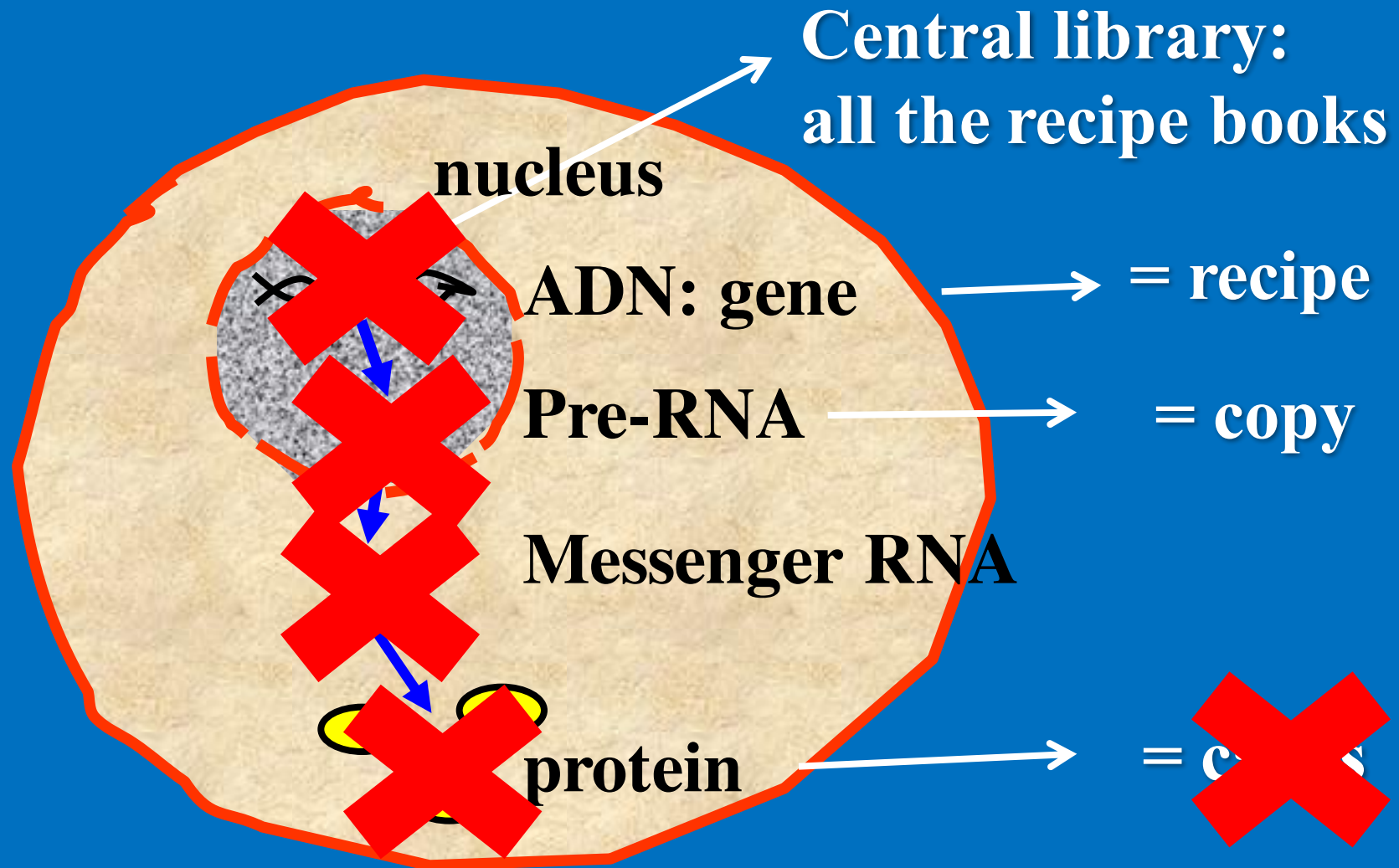


**Get rid
of it!**

Blocking DUX4 protein expression



Many different strategies against DUX4



**At the end of this talk...
you should know what are:**

- ✓ **Chromosomes, DNA, genes and alleles**
- ✓ **Messenger RNAs**
- ✓ **Proteins and DUX4**

- ✓ **Genetic condition for FSHD:**
 - **DUX4 gene in last D4Z4 unit**
- ✓ **Epigenetic condition for FSHD:**
 - **DNA hypomethylation**
 - **Open chromatin**

DUX4
is a
crazy
Chef
and a
muscle
killer



**Get rid
of it!**

Needle!