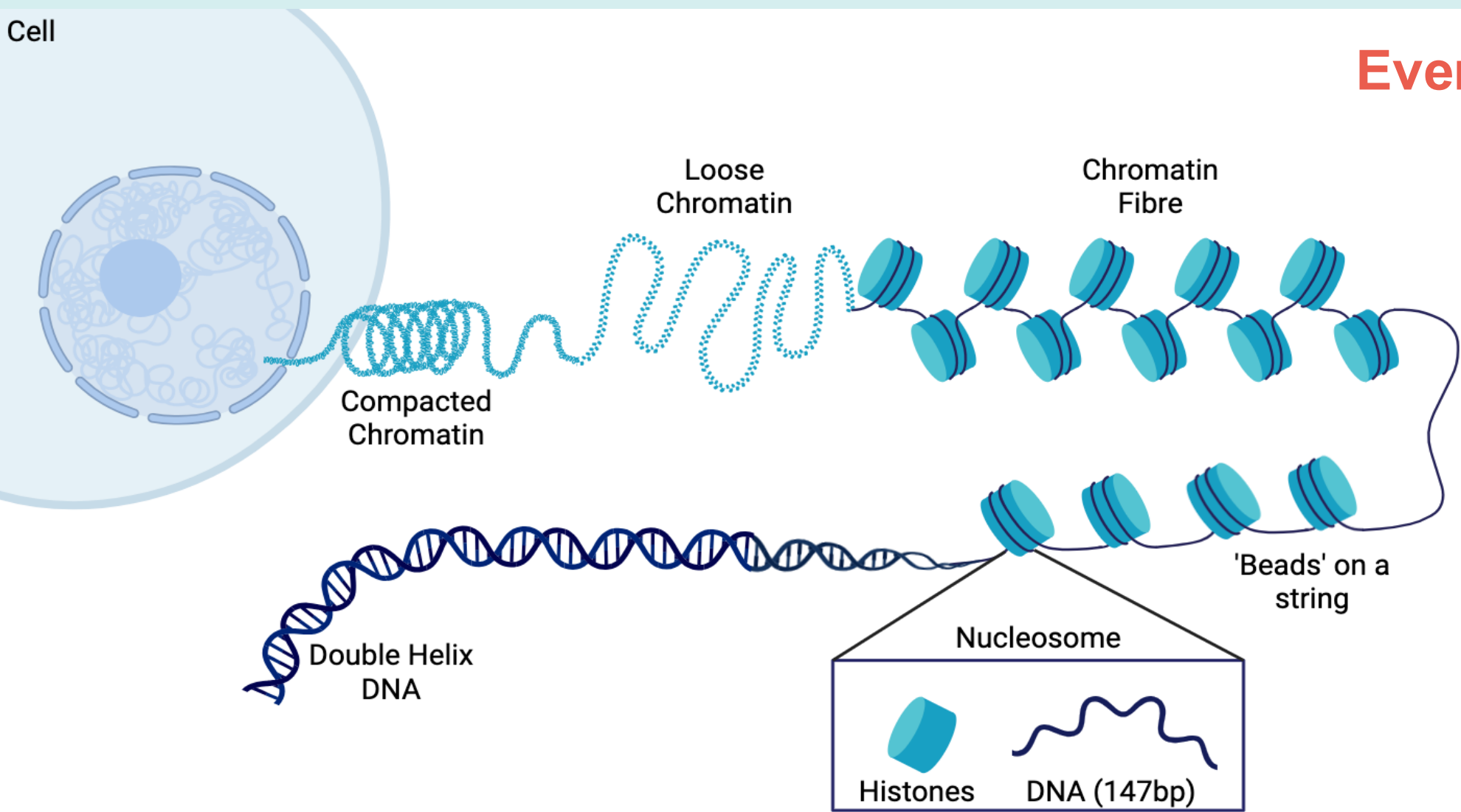


Hidden in the Rare:

What a Rare Form of Anaemia Can Teach Us About How Our DNA Is Packed Inside Cells

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Ever wondered how every cell fits two metres of DNA into a tiny nucleus?

- This remarkable packaging happens through precise folding of DNA into structures called **chromatin**
- The fundamental unit is the **nucleosome**, consisting of DNA wrapped around **histones**, often described as "beads on a string"
- Nucleosomes pack into a 30 nm fiber, which further coils during cell division to form chromosomes

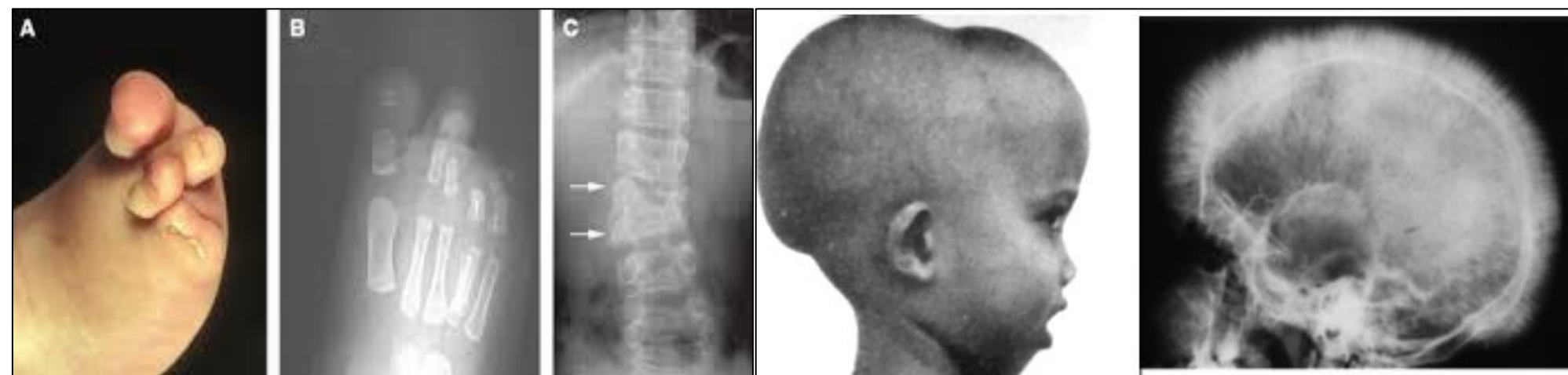
Why? 1) Packaging DNA into the nucleus
2) Controlling gene expression; open chromatin (euchromatin) allows transcription, while packed chromatin (heterochromatin) silences genes
3) Preventing DNA entanglement and damage

What happens when this process goes wrong?

Congenital Dyserythropoietic Anaemia type I (CDA-1): a rare blood disease

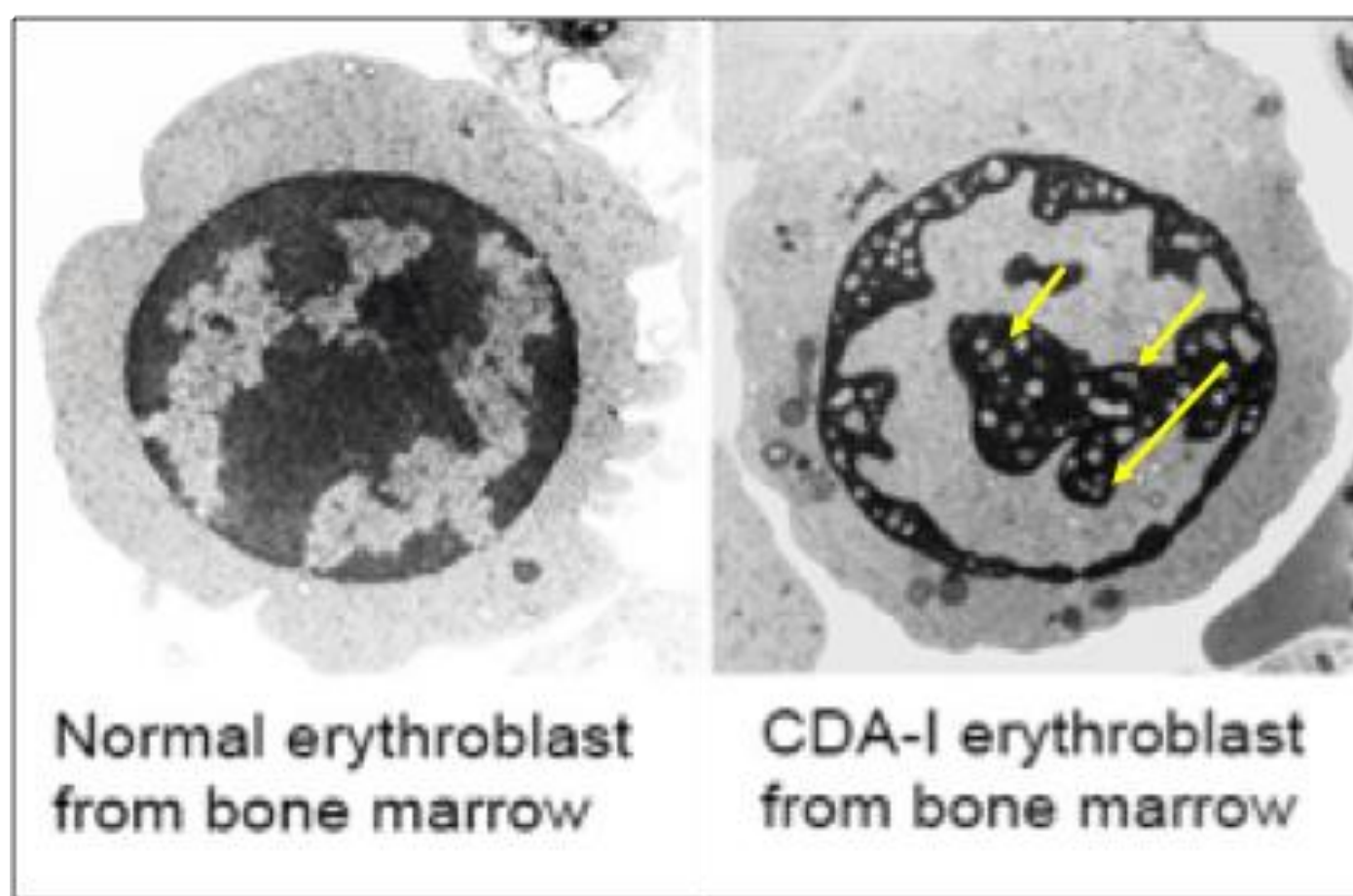
CDA-1 is a rare autosomal recessive anaemia (estimated ~ 1/200 000)

- Splenomegaly, developmental defects, growth retardation
- Normal lifespan but low quality of life



Clinical features of CDA-1

Diagnostic feature: "Swiss-cheese" chromatin



Disease genes in CDA-1:

- CDAN1* (80% of cases) encoding for Codanin-1 protein
- CDIN1/C15orf41* (10% of cases) encoding for CDIN1 protein
- Essential for life

Remaining 10% indicate a possible third locus.

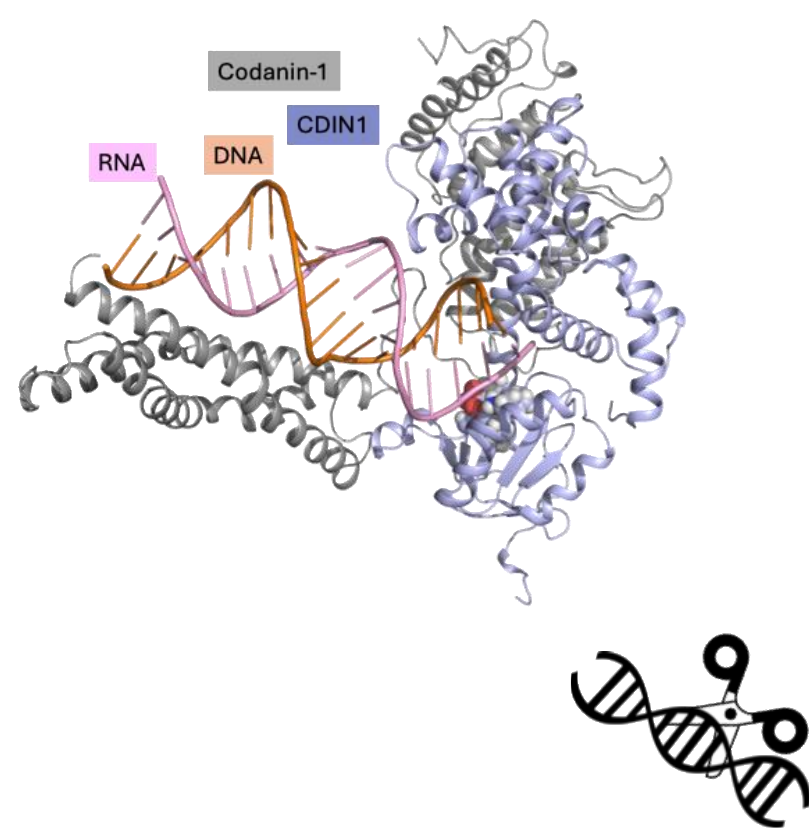


The Role of CDIN1-Codanin-1, the disease proteins of CDA-1

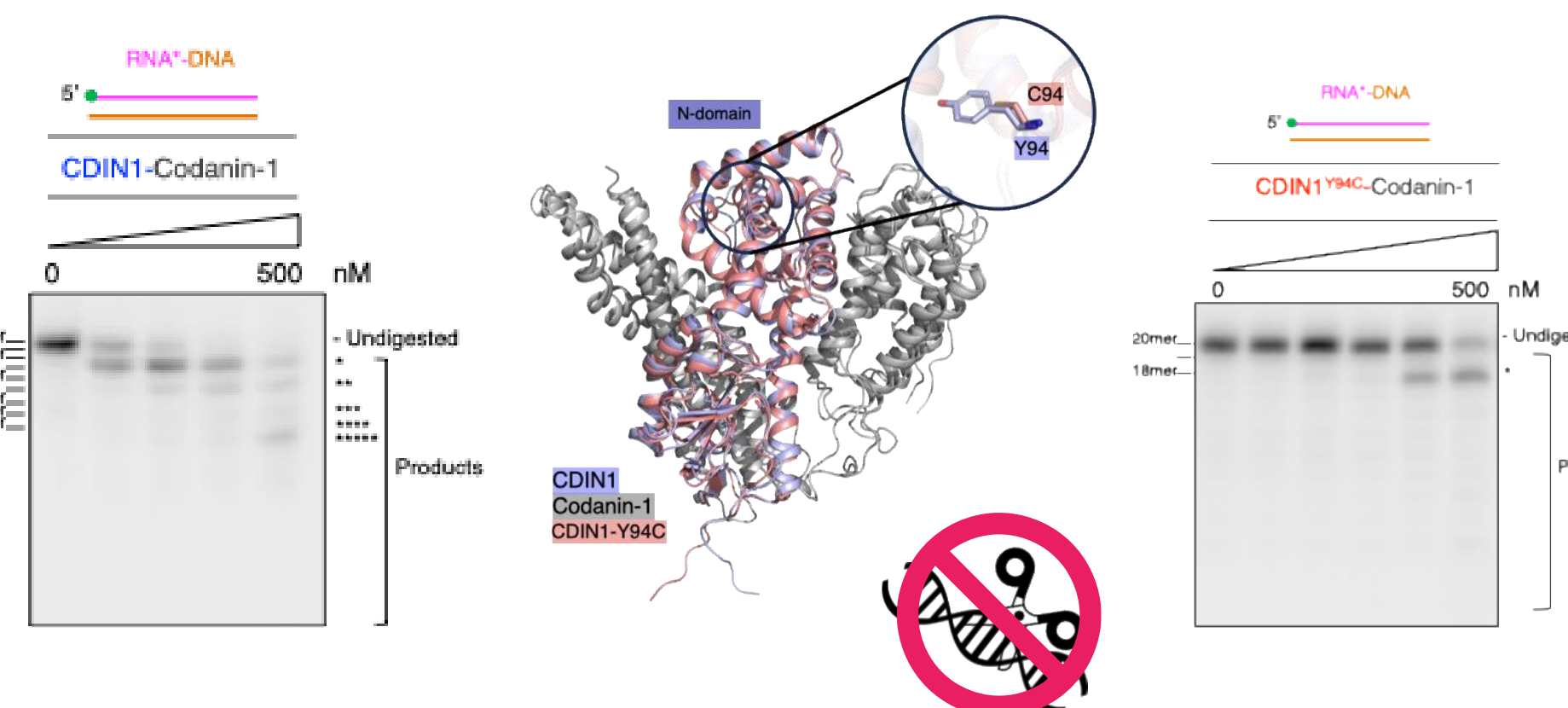
CDIN1-Codanin-1 is a 'molecular scissor' (nuclease):

- Tight complex that has a 'closed' and 'open' form
- In the presence of RNA or DNA, the CC-domain of the complex shifts to accommodate the substrate ('open')
- The complex is now able to cut the substrate

When CDIN1-Codanin-1 functions correctly, it is able to cut RNA into a laddering pattern:

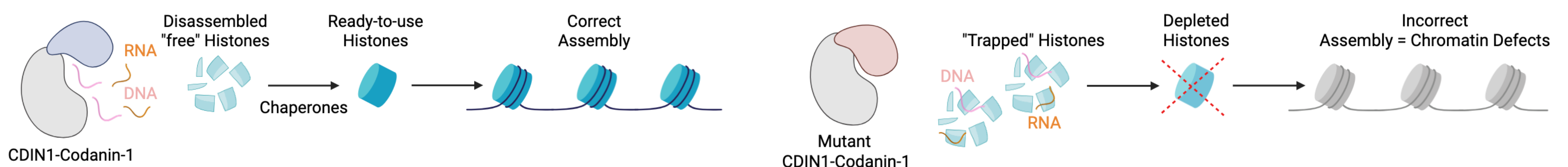


When CDIN1-Codanin-1 has a mutation, it is not able to cut as efficiently:



CDIN1-Codanin-1, 'Swiss-cheese' Chromatin and its importance

- Soluble histones, by virtue of their **positive surface charge**, can attract negatively-charged **DNA and RNA** which 'trap' histones and prevent them from being assembled. There is therefore a need to purge these in order that normal histone deposition can take place
- The CDIN1-Codanin-1 complex **helps clear the DNA and RNA by cutting it** to prevent histones from getting trapped: this assure **correct assembly of chromatin**
- When CDIN1-Codanin-1 is not able to perform its role, chromatin is **incorrectly packaged** and can lead to the 'holes' observed in CDA-1



Studying rare conditions like CDA-1 reveals how our healthy cells work and teach us about essential pathways



CONGENITAL ANAEMIA NETWORK

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