L2 – Introduction to the structure of the genome

Focus of MBLG2071 will be on eukaryotes

Review chemical composition and structure of DNA

DNA is a biopolymer made up of nucleotides (sugar, phosphate & base)
Nucleotides joined together by phosphodiester bonds
DNA double stranded and nucleotides form base pairs

- Purines (2 rings) pair with Pyrimidines (1 ring)
  A = T & G = C

Complimentary bp ➔ antiparallel

Appreciate the need for DNA compaction

Prokaryote

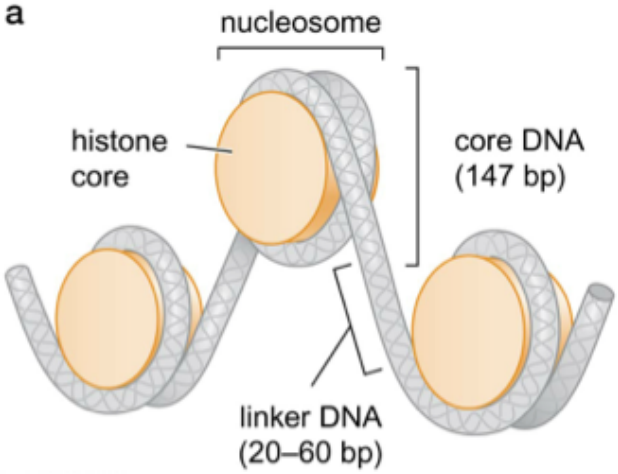
- *E.coli* → one long DNA molecule 1.3mm in length
  → DNA organised into 50-100 independently supercoiled loops
  → RNA & proteins contribute to folded structure = "folded genome"

Eukaryotes

Human cell has 6x10^9 bp of DNA, each bp has a thickness of 3.4Å (3.4x10^-10)
→ Total length of DNA ~2m
- Packaging begins with the formation of **nucleosome**
- DNA wound around small proteins called **histones**

Histones

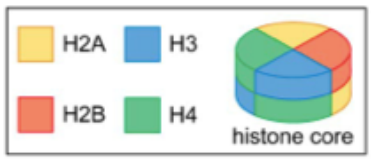
- Have lysine and arginine residues
- +ve at pH 7

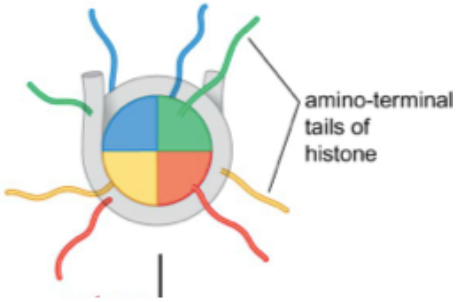


Understand at molecular level the packaging of DNA into chromosomes

There 5 classes of histone (H1, H2A, H2B, H3, H4)

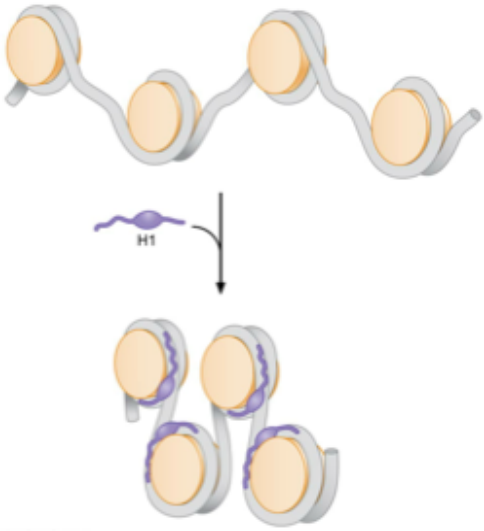
- **Core histones** = H2A, H2B, H3, H4
  - Dimers of each of these together form an **octamer** ➔ makes up protein core of the nucleosome
- **Core DNA** = ~147 bp of DNA that wrap around the core histone
- Nucleosome = DNA + Histone core





The N/C terminal of octamer histone protrude out of the core

<u>Linking nucleosomes and H1</u>



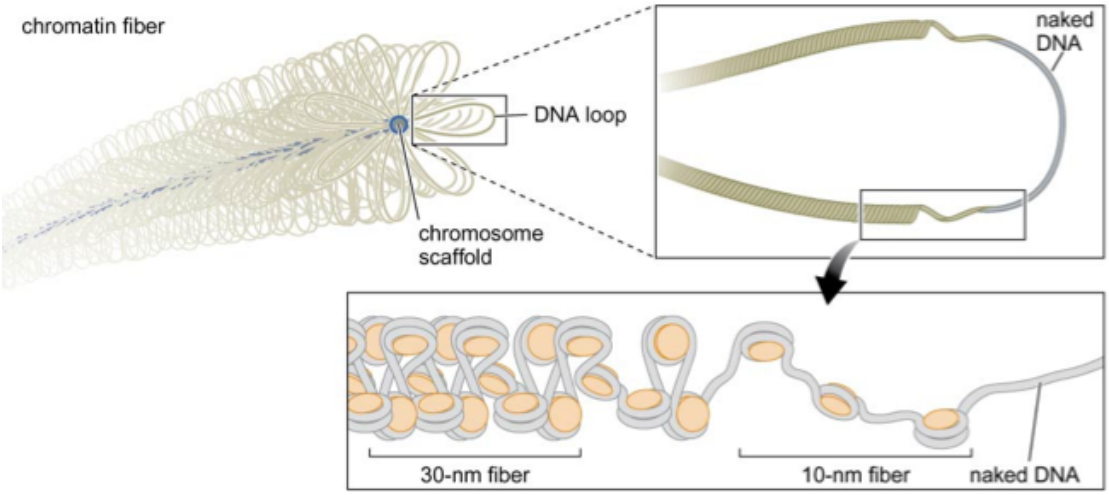
Adjacent nucleosomes are linked by 20-60 bp DNA = **linker DNA**

Histone H1 interact with the linker DNA and part of the core DNA → **linker histone**

- Induces tighter wrapping of DNA in nucleosome
- Formation of 30nm fibre

Loops of 40-90 kbp held together by **nuclear scaffold**

- Higher order packaging not known completely



Summary of packaging

1. Each chromosome contains a single molecule of DNA
2. DNA wrapped around histone core octamer to form nucleosomes
3. Nucleosomes compacted in 30nm fibre by histone H1
4. Higher order packaging not completely understood => loops of DNA held together by nuclear scaffold

<u>Learn about the features of chromosomes</u>

Chromosome = complex of DNA, histones and non-histone proteins

→ Several features allow maintenance & transmission to next generation

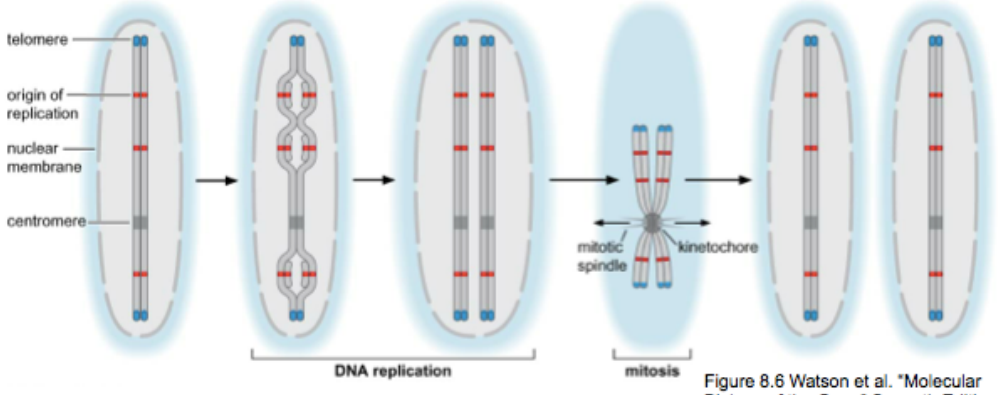
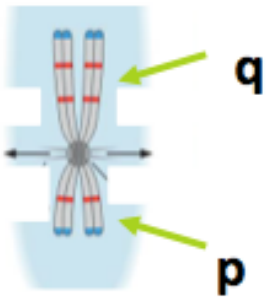


Figure 8.6 Watson et al. "Molecular Biology of the Gene" Seventh Edition

Origin of replication

- Specific genomic DNA sequences direct the initiation of DNA rep.
- Bacterial chromosome had 1 origin of replication
- Eukaryotes have origins of replication every 30-40 kbp throughout the length each chromosome

Centromere

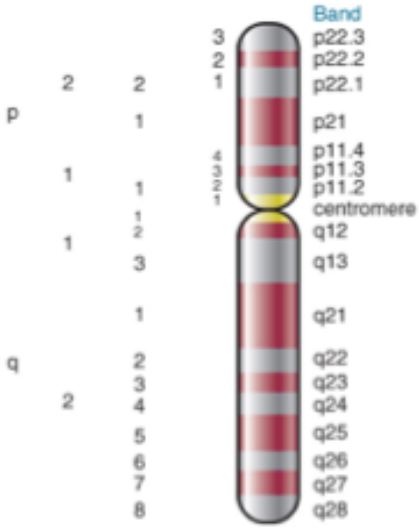


- Responsible for segregation of chromosomes at mitosis & meiosis
- Contain large amounts of repetitive sequences
- Reference point/landmark → define the position of markers on a chromosome
- Divides chromosome into 2 arms
  - Arms are not the same length, one long & one short
  - Short arm = **p** (petit)
  - Long arm = **q**

Telomere

- Located at the ends of chromosomes
- Consists of simple repeating structure
- Allow ends of chromosomes to be replicated

Chromosome stains/staining techniques

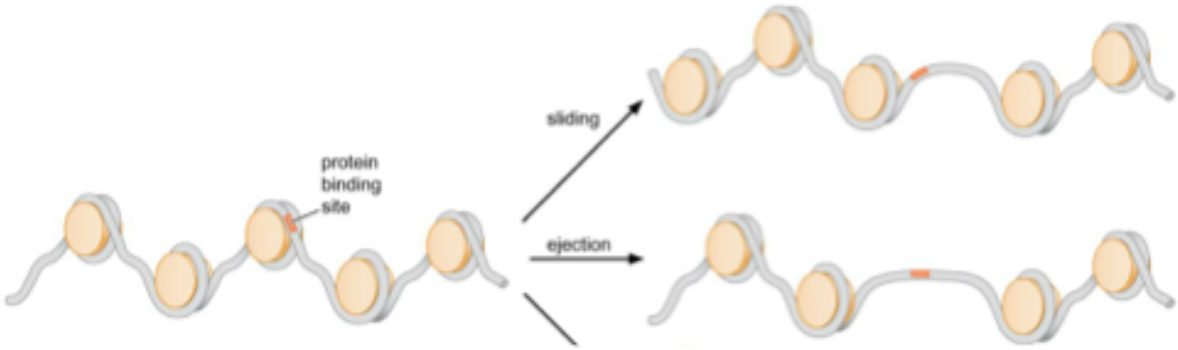


- **Giemsa**
  - Chemical preventing mitotic spindle from pulling apart
  - IDing chromosome and detecting abnormality in chromosome
  - G-bands = reference point of locating gene, determine position → create chromosomal map
- **Feulgen**
  - IDing chromosomal material/DNA in cell
  - Dark staining = heterochromatin, region of dense DNA packaging, consisting of multiple repeats
  - Weak stain = euchromatin, DNA loosely packaged, active in transcription

Learn how DNA packaging relates back to phenotypic function of DNA

- Even in euchromatic regions, DNA is associated with histones
- How does transcription factor + other regulatory proteins gain access to DNA?
- Association of DNA with histone octamer is dynamic
- Non-covalent interaction → release and rebinding

<u>Chromatin remodelling</u> → moving nucleosomes



- Performed by large protein complexes = nucleosome remodelling complexes
- Derive energy from hydrolysis of ATP
- 2 types of modification
  - Sliding
  - Displacement/ejection

<u>Chromatin modification</u> → adding/removing chemical groups from histone proteins

- Each of the histone proteins in the core octamer has an N-terminal tail, which can be post-translationally modified ➔ determines how accessible the DNA is.

Histone **acetylation** and **deacetylation** are processes by which lysine on the N-terminal tail protruding from the histone core of the nucleosome are acetylated and deacetylated as part of gene regulation

- Histone acetylation controlled by histone acetyl transferase (**HAT**). It adds acetyl group to lysine residue, causing it to go from +ve charge to neutral. This in turn cause uncoiling of the –ve DNA (since lysine is no longer +ve), allowing genes to be accessible to transcription factors ➔ become euchromatic, able to synthesis new DNA
- Likewise, histone deacetylase (HDAC) removes the acetyl group → lysine becomes +ve again, DNA coils around the histone once again. ➔ heterochromatin (dense DNA packaged region)