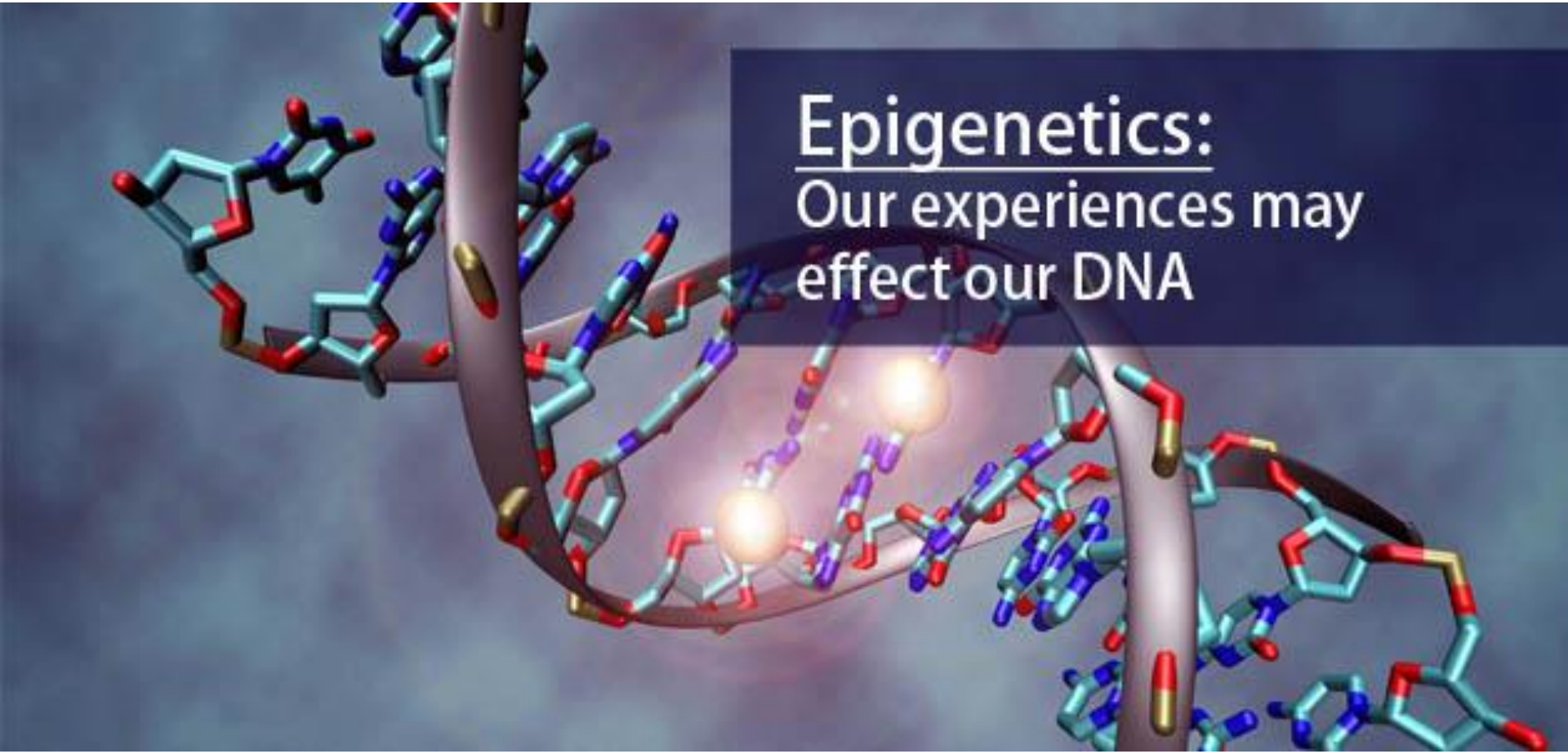

Epigenetics:
Our experiences may
effect our DNA

Neurodegenerative disease

Parkinson's:

Depletion of dopaminergic neurons in substantia nigra

Tremors, rigidity, slow movement.

Key defective genes identified in inherited (familial) PD:

-SNCA associated with lewy bodies)

-PARK2

Alzheimer's

B amyloid deposits toxicity

Memory failure, confusion, language difficulties and withdrawal.

Mutations in familial AD include:

-PSEN1

-PSEN2

-APP

Huntington's

First and most studied genetic disease

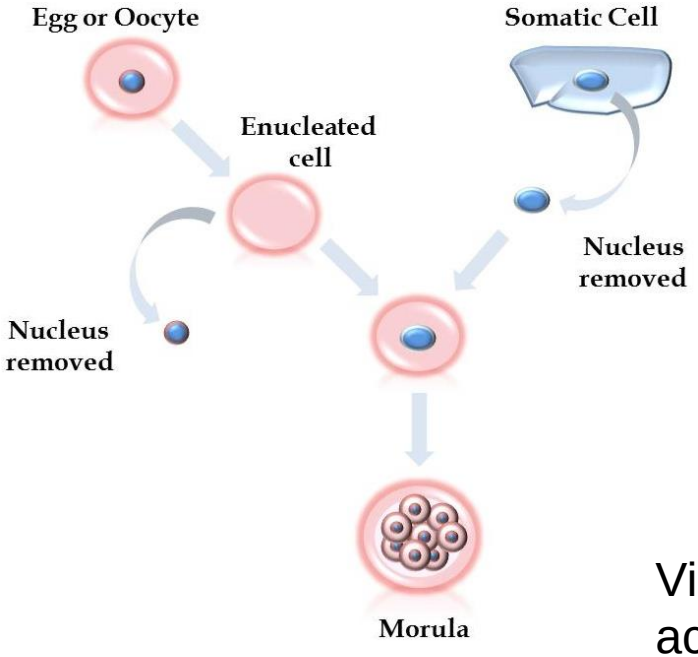
Caused by dominant mutation with an increased number of glutamine (G) codons within the gene *HTT.*

Affects muscle coordination, leads to psychiatric and cognitive decline.

Epigenetics

Allow us to explain differentiation and induced pluripotency.

John Gurdon's experiments on frogs demonstrated that differentiated cells could give rise to undifferentiated cells

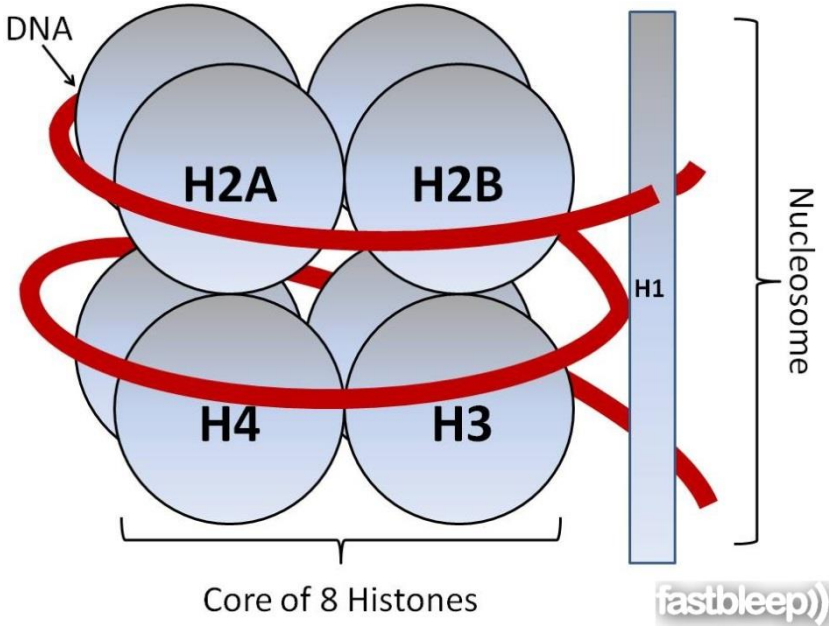


<u>Modifications are heritable</u>

Epigenetic modifications are what increase or decrease gene expression, and therefore regulation differentiation of cell types.

Via the following mechanisms; methylation, histone acetylation and miRNA regulation.

Histone modifications



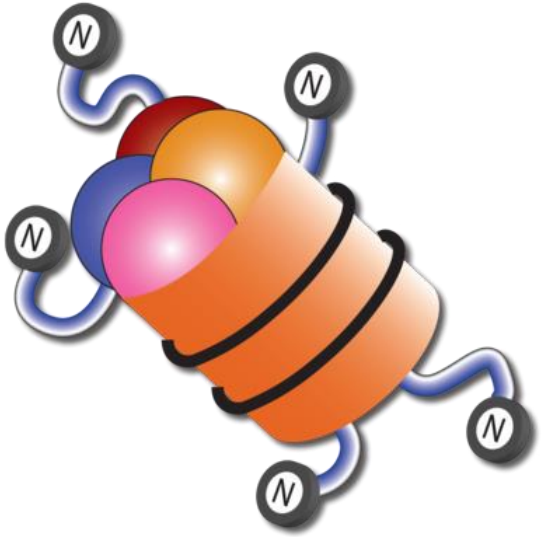
Lysine Acetylation:

-Addition of an acetyl group to lysine (on Histone tails) neutralises positive charge.

-lesser attraction between histones and DNA.

-Looser chromatin structure means more accessible for transcription

Histone acetyl transferases (HATs) and Histone deactylases (HDACs) are involved with the addition and removal of acetyl groups

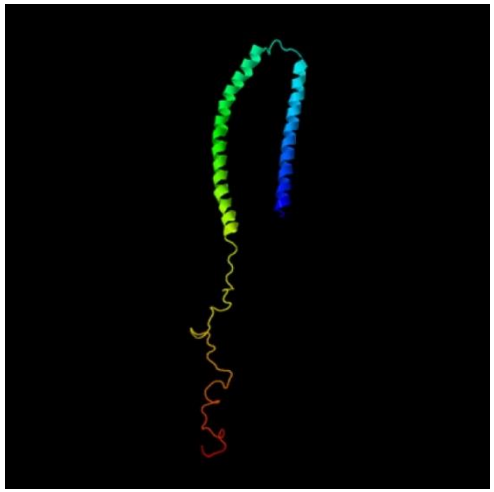


Histone mods in context

In Parkinson's:

-α synuclein associates with the Sirt2 histone deacetylase to prohibit histone acetylation.

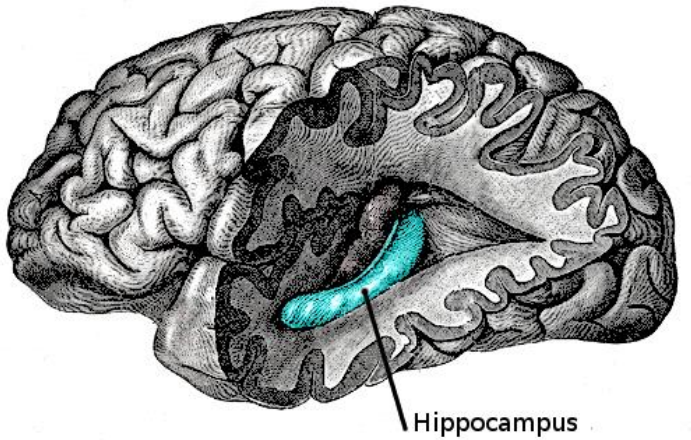
--many modifications to H3 in animal models of PD have been reverted by levo-dopa treatment



In Alzheimer's:

-hypoacetylation of histones

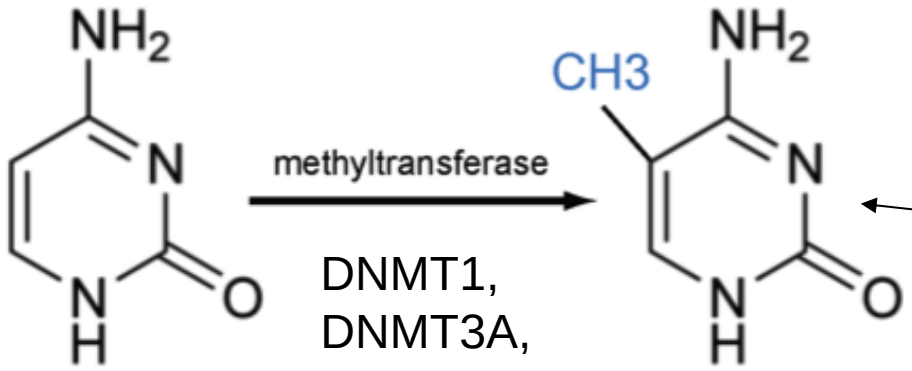
-phosphorylation of H3 in hippocampus



In Huntington's, other than increased Histone methylation, decreased acetylation has also been studied.

DNA Methylation

Cytosine



DNMT1,
DNMT3A,

DNMT3B

5-Methylcytosine

Most frequently seen on CpG islands

MeCP2 (Methyl CpG binding protein 2) binds to DNA in gene promoter.

Attracts other proteins to ‘switch off’ gene; transcription machinery cant access DNA so mRNA molecule is not produced – no protein synthesis.

Methylation in context

In Parkinson’s

Methylation contribution unclear, but:

-hypomethylation of SNCA intron 1 in several brain regions

-α synuclein reduces DNA methyltransferase 1 (DNMT1) activity

In Alzheimer's:

-Reduced methylation in MZ twins with Alzheimer's study.

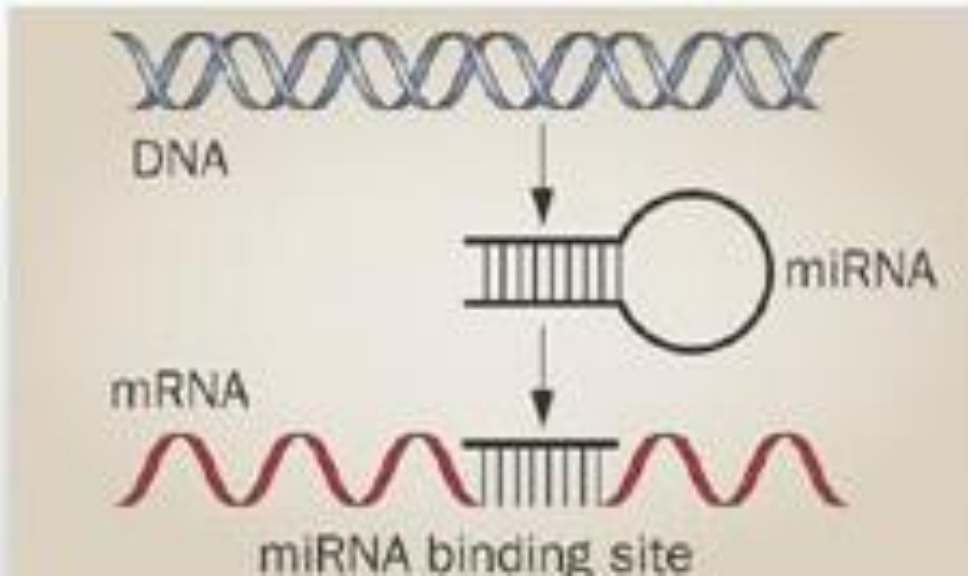
-Hypomethylation of TMEM59, linked to amyloid β peptide production.

In Huntington’s:

Overall increased methylation of histones in both models and patients.

DNA methylation is the addition of a methyl group (M) to the DNA base cytosine (C).

miRNA regulation



-small RNA molecules (of only 21 nucleotides long);

-attach to mRNA molecules at non coding regions (3' UTR and 5'UTR).

-if bonding occurs perfectly within key region (2-8 nucleotides), mRNA destroyed by enzymes.

-imperfect match inhibits mRNA

miRNA mods in context

In Parkinson's:

-miR-133b has specific expression to midbrain dopaminergic neurons

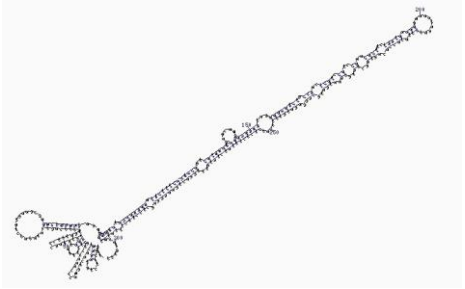
-miR-7 represses expression of SNCA

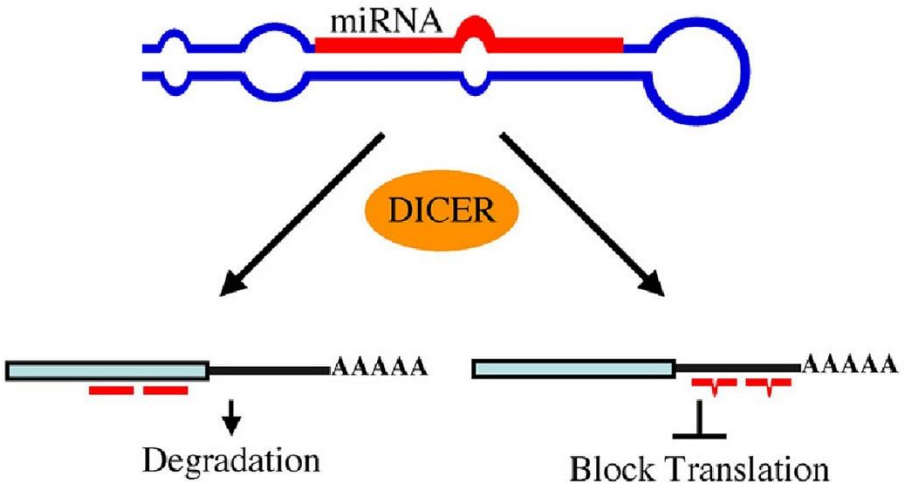
-global down regulation of miR-34b/c

In Alzheimer's:

-reduction of miR-101 & miR-16 lead to down regulation of amyloid protein expression

-under expression of miR-124 lead to inclusion of exons 7 & 8 in amyloid precursor protein.

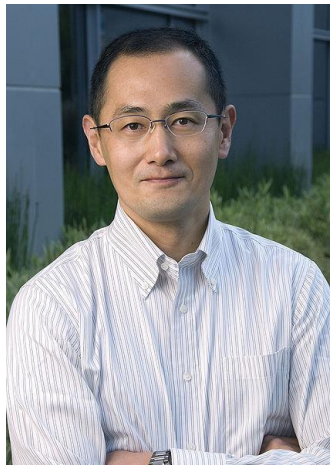




In Huntington's:

Five different miRNA molecules have been implicated in causing HD but the mechanism of this is unclear.

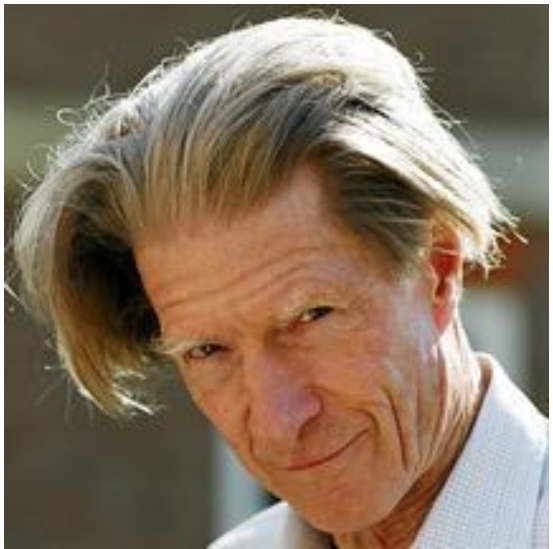
Conclusion



Epigenetics is a valuable study for understanding pathology and future treatments

Lots of insight provided for all aspects of disease, life and inheritance.

Already had two Nobel Prize wining contributors: Yanamaka and Gurdon.



Hope you enjoyed!