WHAT THESE NOTES INCLUDE

- Table of content that allows easy electronic navigation
- Lecture content translated into comprehensive notes that are easy to understand. You do not need to attend or watch any lectures with these notes.
- Integration of useful video links that help you understand concepts poorly explained in lectures
- Tips on memorising content when applicable (see below for a preview)
- Brief practical notes on experiment 1 & 2 for BCHM3071 and BCHM3971
- Tips on studying for final exam and insight/feedback into 2018 final exam. Insight includes what you should prioritise when studying.

Lecture 10 – Parental/Genomic Imprinting

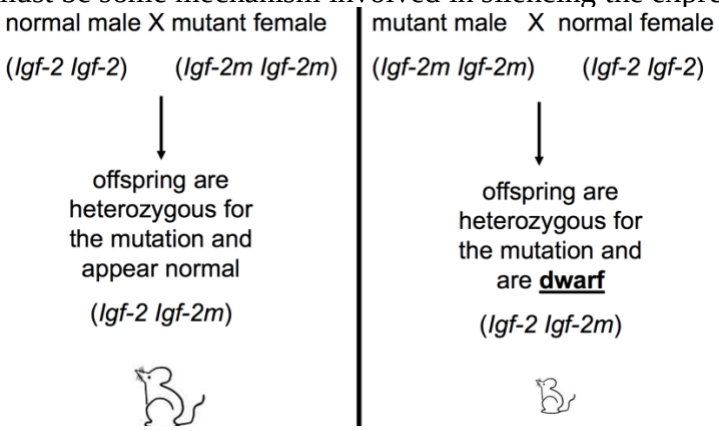
***From lecture 9* – paternal X chromosome in marsupials is always inactivated, how is this selection of inactivation regulated/determined?** This is achieved by 'imprinting' the paternal chromosome.

Parental/genomic imprinting is a form of epigenetic modification of a particular allele of a gene that is inherited from parent(s) that also had the gene modified epigenetically.

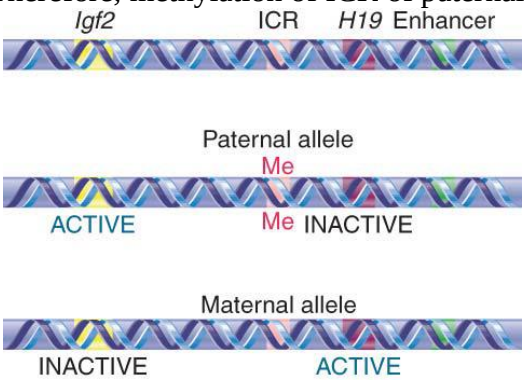
- As a result, mono-allelic expression occurs (this is rare because usually expression from both parental alleles occur)
- These changes of a particular allele of a gene are maintained throughout cell division, thus are not random.
- Imprinting involves methylation of CpGs located in nearby segment of DNA known as **differentially methylated domain (DMD)** or **imprinting control region (ICR)**
- However, **methylation of these regions does not always lead to gene silencing** (see example below)
- Methylation of imprinted genes occur prior to fertilisation and are not de-methylated when embryonic stem cells are 'wiped-clean' but DNA de-methylase
    - Methylation done by DNMT3a and DNMT3b

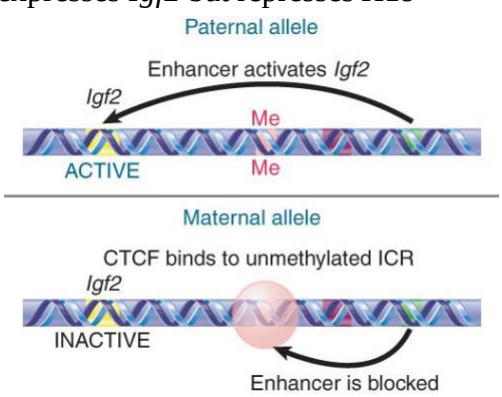
Example: Insulin-like Growth Factor (Igf-2)

- *IgF-2m* is a defective mutant and phenotype (dwarfism) displays **only when the paternal allele is mutated.** Thus, there must be some mechanism involved in silencing the expression of the maternal allele



- Studies have that the imprinting control region (ICR) of the paternal allele is actually methylated.
- This is because an enhancer-inhibitor protein known as CCCTC-binding factor (CTCF) binds to the ICR when its **unmethylated**. So, when it is methylated, the enhancer can loop to the promoter leading to gene expression of *Igf2*.
- Additionally, when the enhancer element cannot loop to the promoter of *Igf2*, it loops to the promoter of *H19* instead (downstream of ICR, so binding of CTCF does not affect it, see images below). This promotes gene expression of *H19*
- Therefore, methylation of ICR of paternal allele expresses *Igf2* but represses *H19*





Human syndromes arising from defects at imprinted loci

Prader-Willi and Angelman syndrome are characterised together because affected genes are located on chromosome 15

- **P**rader-Willi syndrome arises when the **p**aternal allele is deleted/imprinted
  - No expression of *MAGEL2* or *SNRPN*
  - Symptoms include hyperphagia, obesity and shortness. *Tip to remember this: prader rhymes with darth vader who's a chubby little kid who has hyperphagia*
- Angel**m**an syndrome arises when the **m**aternal allele is deleted/imprinted
  - No expression of *UBE3A*
  - Symptoms include uncontrollable & inappropriate laughter, seizure, speech impairment and delay. *Tip to remember this: visualise a laughing angel with a crown (seizing(ure) the throne)*

PATERNAL
Prader-Willi

MATERNAL
angelMan

Beckwith-Wiedermann (BWS) and Silver Russell syndrome (SRS)

- BWS: pre- and postnatal growth greater than the 90th percentile
  - ICR of both alleles are methylated which over-expresses both *Igf2*
- SRS: pre- and postnatal growth retardation
  - ICR of both alleles are **not** methylated, so no *Igf2* is expressed
- Trend in imprinted genes: imprinted paternal genes promote growth and maternal genes retrain growth