Methylation and Human Disesases

Joint Graduate Seminar
The Chinese University of Hong Kong
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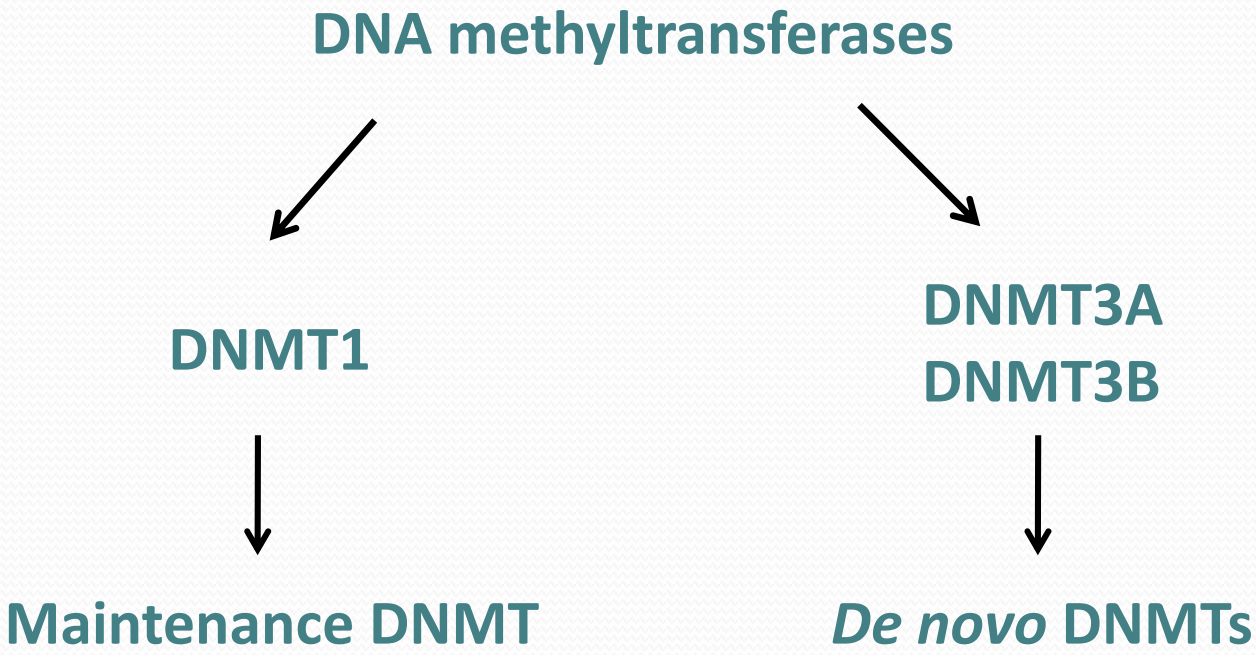
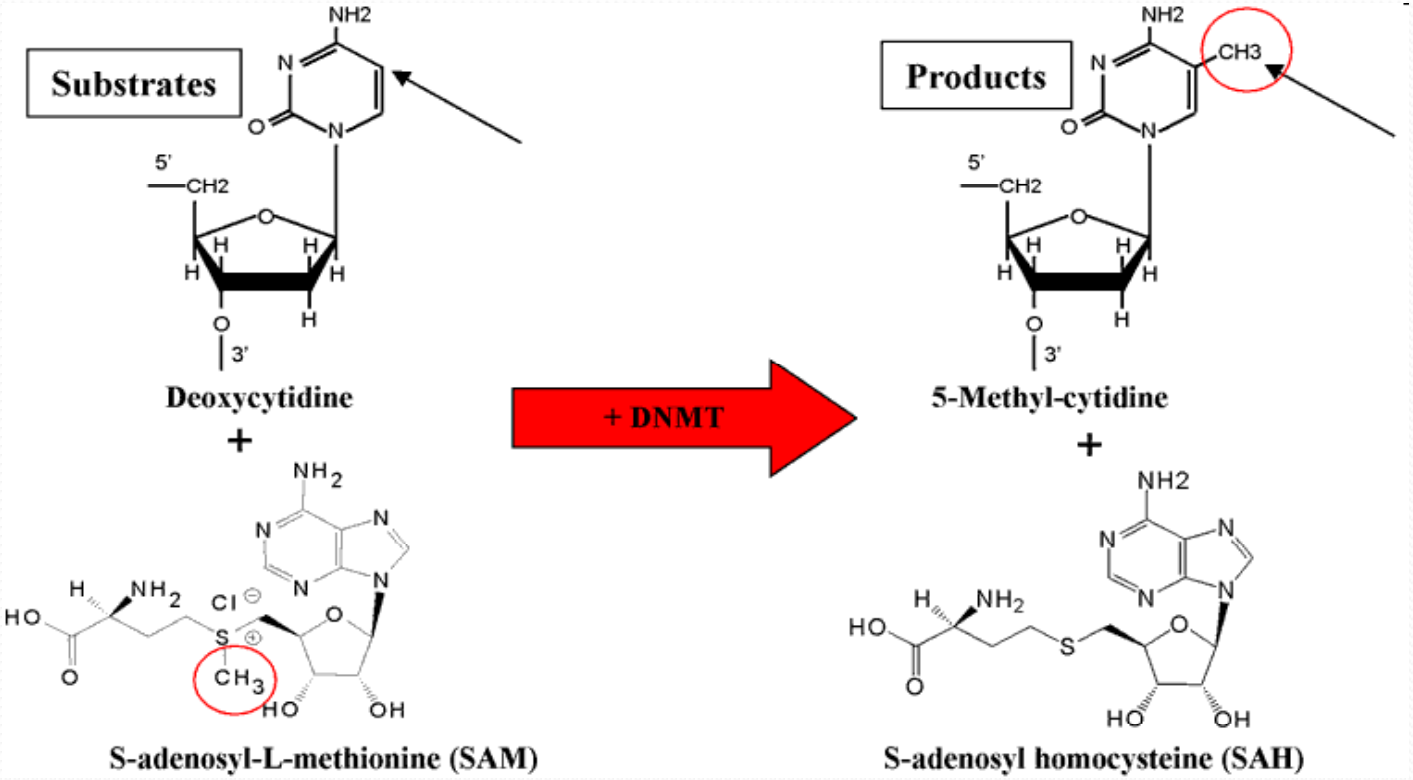
What is Methylation?

- Epigenetics
- Heritable, stable, reversible
- Catalyzed by DNA Methyltransferases (DNMTs)



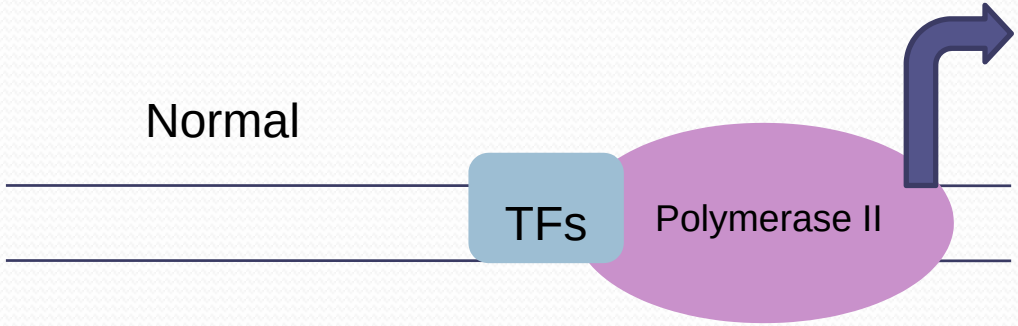
Where Does Methylation Occur?

- At cytosine residues of **5'-CpG-3'**
- CpG islands mostly encompass gene promoters

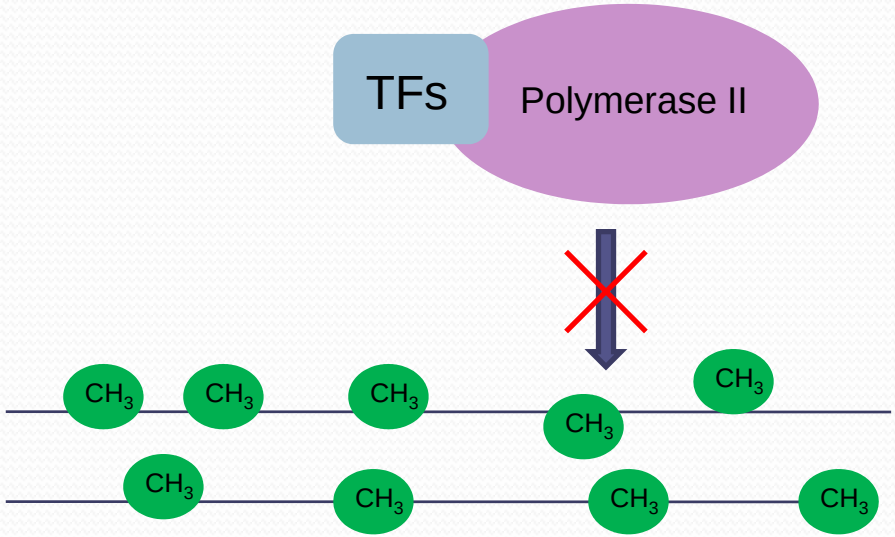


http://www.med.ufl.edu/biochem/keithr/fig1pt1.html

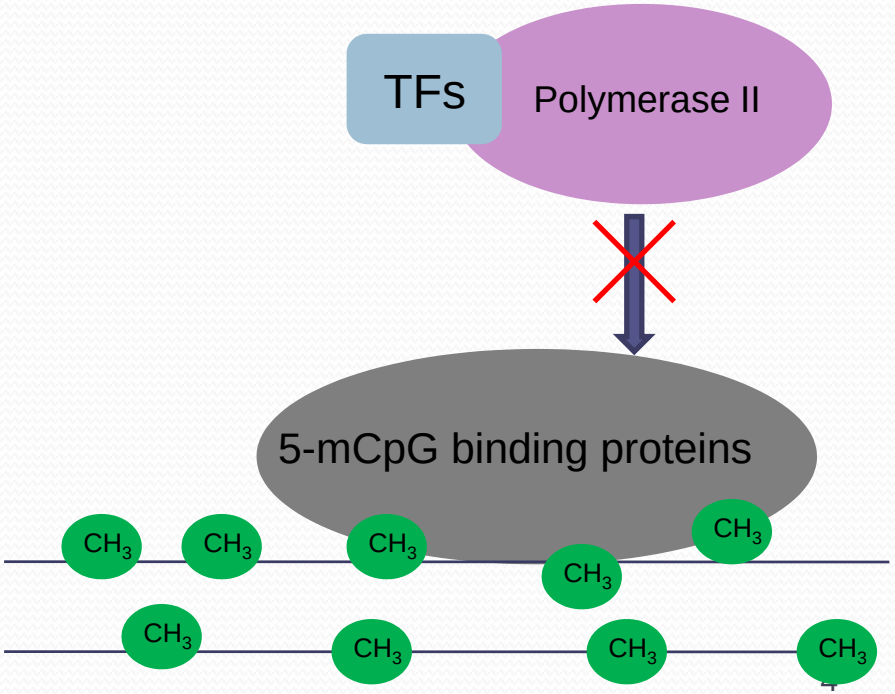
Silencing Effect of Methylation



Direct Inhibition of TFs binding



Inhibition of TFs binding by recruitment of MeCPs



Roles of Methylation

- Essential in normal development
  - Regulates gene expression and chromatin structure
  - Genomic imprinting
  - X-inactivation in females
  - Defense mechanism

- Deletion of any DNMTs is lethal in mice

Genetic Diseases Caused by Methylation Defects

- Mutations in proteins involved:
  - ICF
  - Rett Syndrome
- Defects of imprinted genes on chromosome **15q11-13**:
  - Prader-Willi Syndrome
  - Angelman Syndrome
- Loss of imprinting:
  - Beckwith-Wiedemann Syndrome

ICF Syndrome

(Immunodeficiency, Centromeric instability, Facial anomalies)

- Mutation in **DNMT3B**

Clinical features:

- Combined immunodeficiency
- Developmental delay
- Mental retardation

Rett Syndrome (RTT)

- Mutation in **MeCP2**
- X-linked neurodevelopmental disorder

Clinical features:

- Mental retardation
- Autistic behaviour
- Stereotypical hand movements
- Seizures

http://www.gfmer.ch/genetic_diseases_v2/index.php

Prader-Willi Syndrome (PWS)

Clinical features:

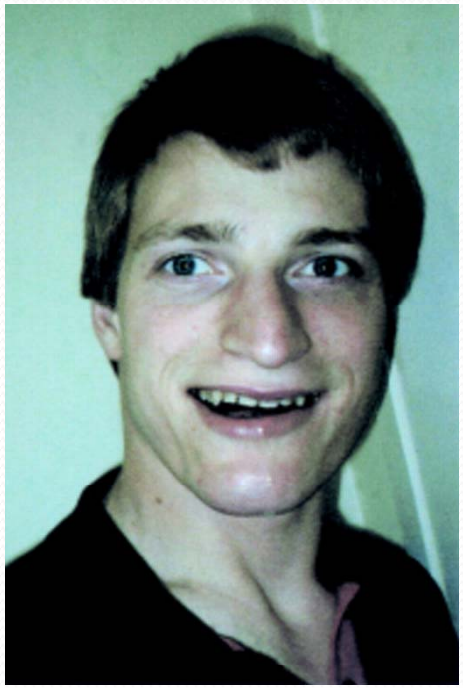
- Mental retardation
- Slow moving
- Obesity
- Hypogonadism
- Small hands and feet

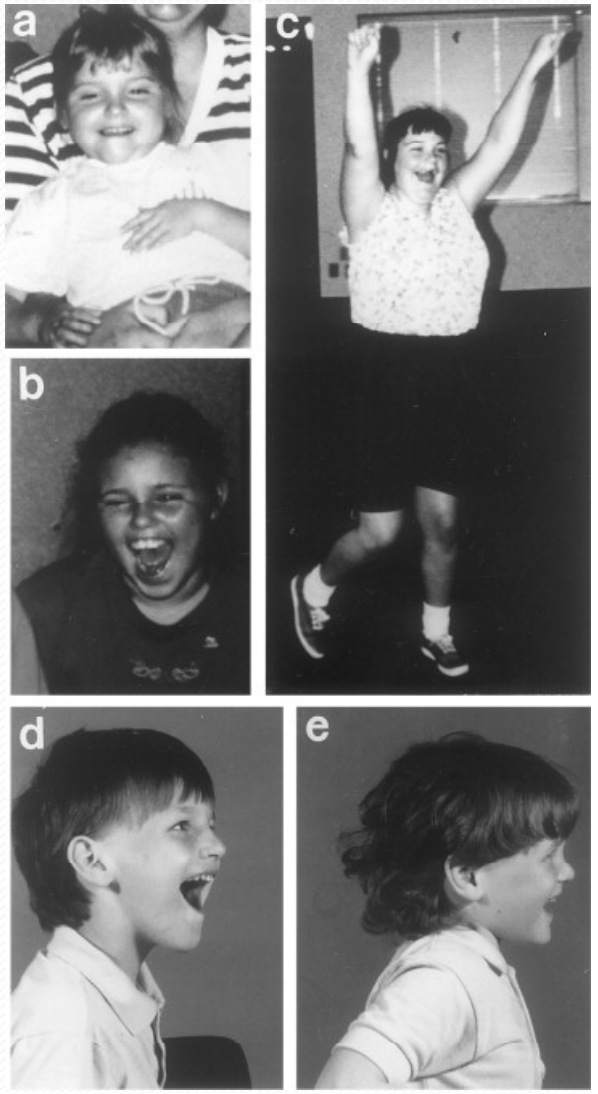
http://medgen.genetics.utah.edu/

Angelman Syndrome (AS)

Clinical features:

- Severe mental retardation
- Hyperactive
- Disordered movement
- Uncontrolled laughter
- Dysmorphic facial features





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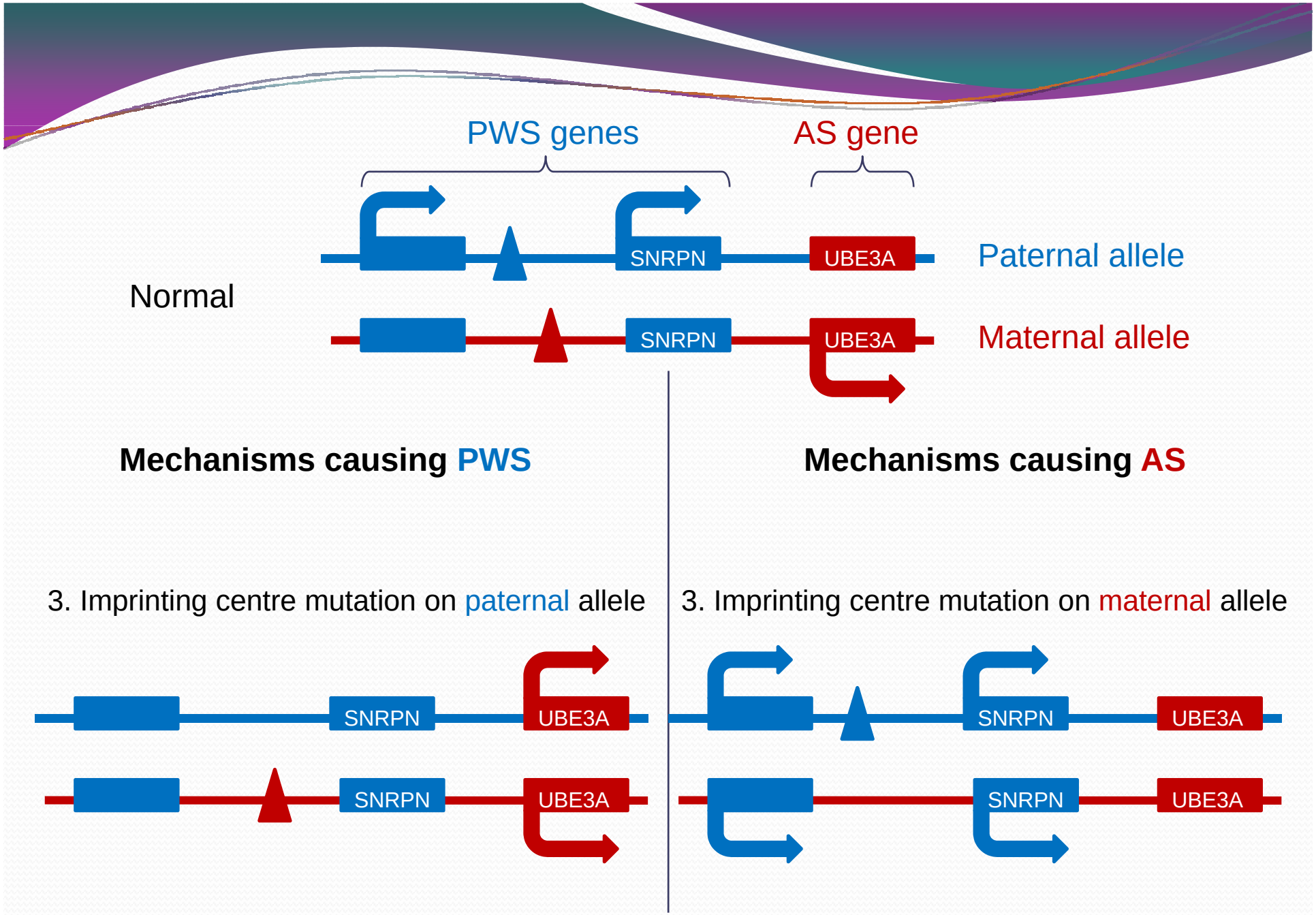
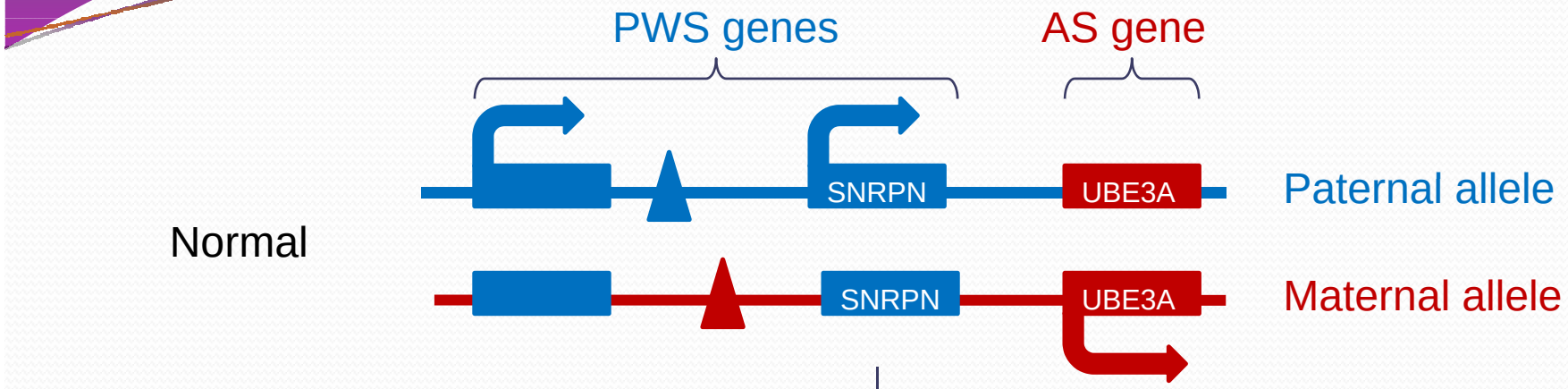
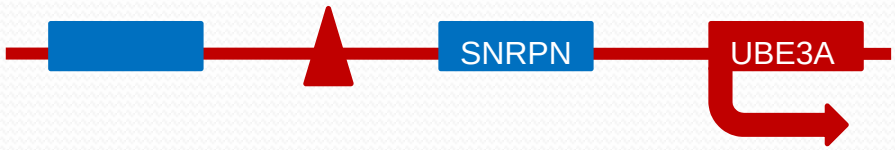


Adapted from Hitchins, M.P. and Moore, G.E. Genomic imprinting in fetal growth and development. Expert Rev Mol Med. 2002 May 9;4(11):1-19.



Mechanisms causing PWS

1. Deletion of paternal 15q11-13



Mechanisms causing AS

1. Deletion of maternal 15q11-13

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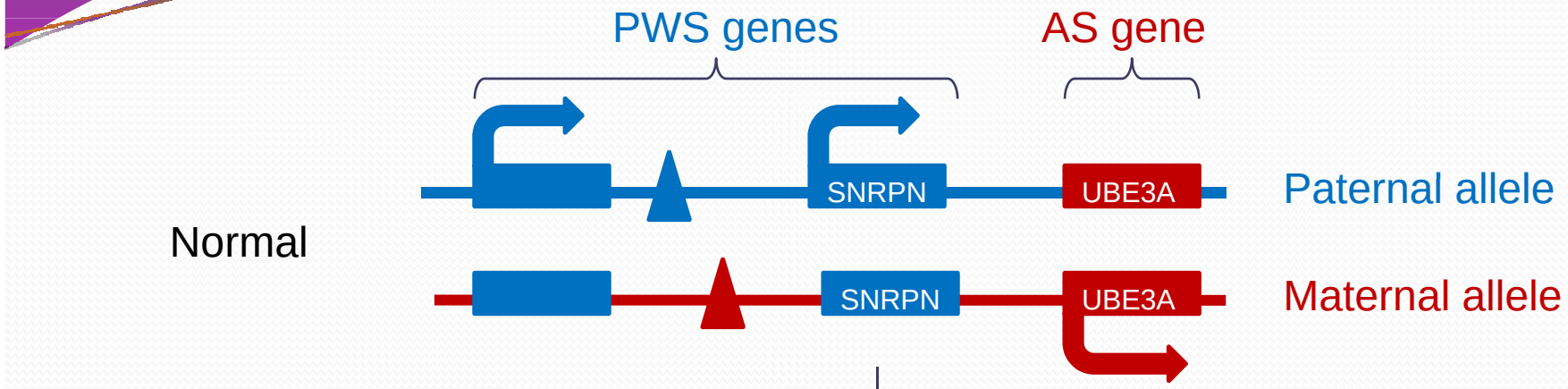
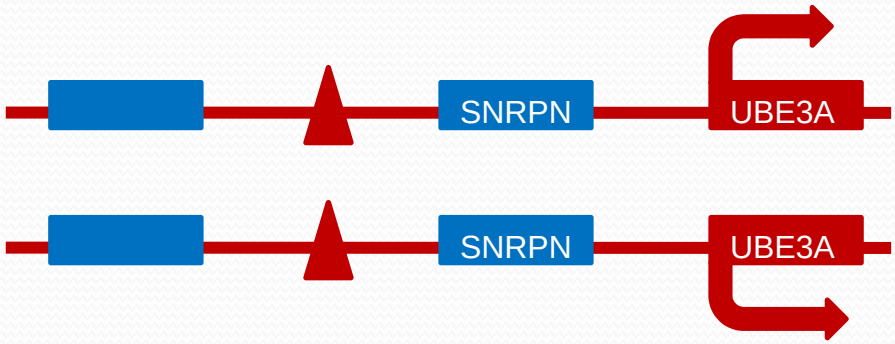


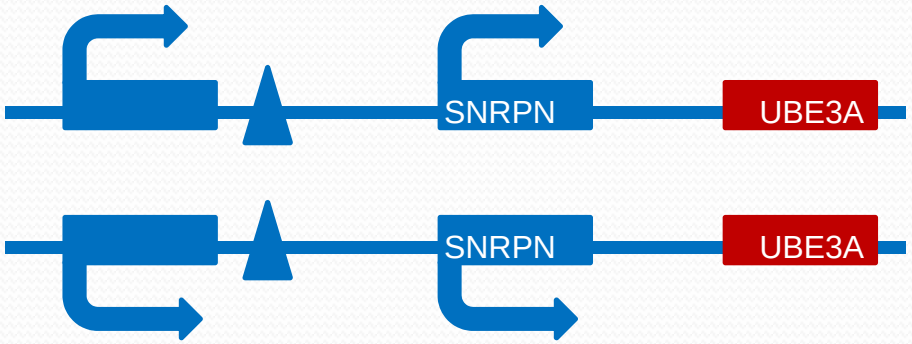
Mechanisms causing PWS

2. Maternal uniparental disomy



Mechanisms causing AS

2. Paternal uniparental disomy



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Beckwith-Wiedemann syndrome (BWS)

- Loss of imprinting of **IGF2** gene

Clinical features :

- Macroglossia (large tongue)
- Macrosomia (birth weight and length >90th percentile)
- Umbilical hernia (midline abdominal wall defects)
- Ear creases / ear pits

http://www.gfmer.ch/genetic_diseases_v2/index.php

Methylation and Cancers

- Cancers once viewed as genetic disorders
- Epigenetic events also responsible
- 2 types of methylation pattern defects:
  - Genome wide **hypo**methylation
  - Gene specific **hyper**methylation

Hypomethylation

Oncogene activation

Retrotransposons activation

Chromosome instability

Loss of imprinting

Loss of Imprinting of IGF2 in cancers

Normal	Cancers (e.g. colorectal cancer, Wilm's tumour)
Methylation	Hypomethylation
↓	↓
Imprinted	Loss of imprinting
↓	↓
Expression of IGF2 from paternal allele	Expression of IGF2 from both alleles
	↓
	Transformation

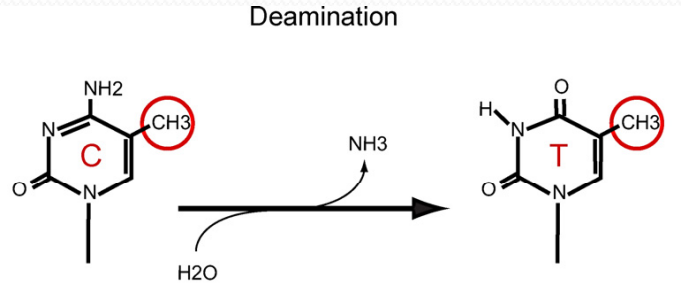
Hypermethylation

Inactivation of TSGs, DNA repair genes

Increased mutability of 5-mC

Altered repair efficiency

Differential cell division rate



Most Frequently Reported Genes Hypermethylated in Cancers

TSGs	Function	Cancer type with hypermethylation
p16-INK4	Cell cycle arrest	Lung, liver, leukemia, lymphoma
RASSF1	Cell cycle regulation	Ovarian, thyroid, cervical, kidney
MGMT	DNA repair, drug resistance	Brain, colorectal, lung, gastric
CDH1	Cell-cell adhesion	Gastric, lung, leukemia
MLH1	DNA mismatch repair	Gastric, colorectal
APC	Apoptosis	Lung, breast, prostate

Methylation and Oncogenic Viruses

- Viral oncoproteins can silence host genes that interfere with cancer progression
  - E.g. LMP1 of EBV activates DNMTs and downregulates E-cadherin
- Hypermethylation identified in viral genomes
  - E.g. EBV, HPV, HBV
- Possible roles:
  - Evasion of host immune system
  - Establishment of latent infections

Methylation Patterns as Cancer Biomarkers

- Defects found in almost all cancer types
- Patterns specific in different tumours
- Possible biomarker for early detection of cancers
- Predict metastatic potential and therapy sensitivity

Epigenetic Therapy

- Reversibility of epigenetic events can be targets of therapy in cancer
- DNMT inhibitors:
  - 5-Aza-cytidine
  - 5-Aza-2'-deoxycytidine
- In vitro, diminish activities of DNMTs and induce demethylation of TSGs

The End

Thank You!