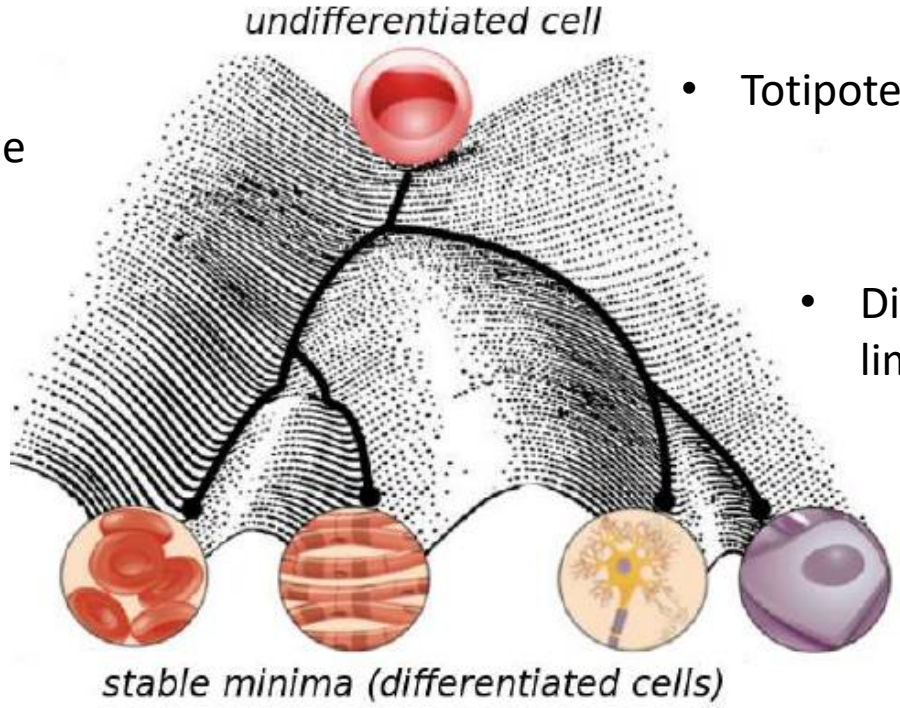
Epigenetics

- Genomic imprinting and X chromosome inactivation

AS3323/5621
Lecture 25
Dec, 4th 2018

Epigenetics

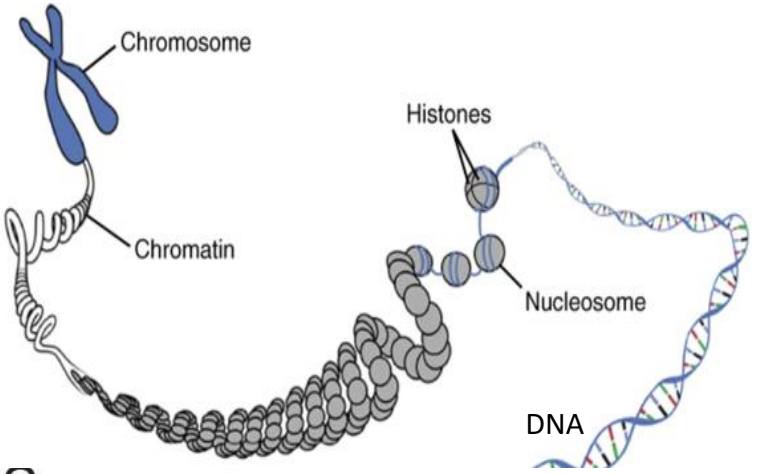
C.H. Waddington
1942
Epigenetics landscape



- Totipotent state
- Differentiation potential is limited
- Cell fate is established

- Epigenetics: changes above or in addition to genetics to explain differentiation

Epigenetics



GENETICS

DNA

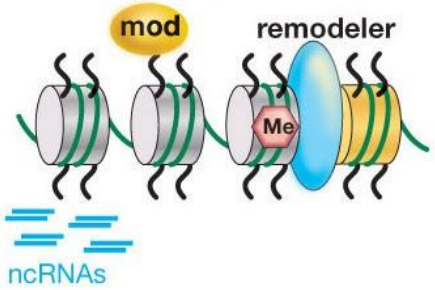
mutations

inherited

germ line

EPIGENETICS

alterations



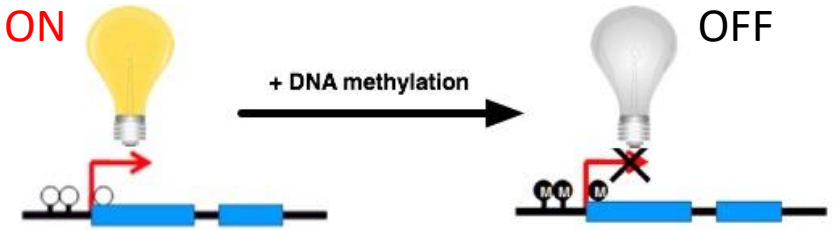
- **DNA methylation**
- **Histone modification**
- **Non-coding RNA**

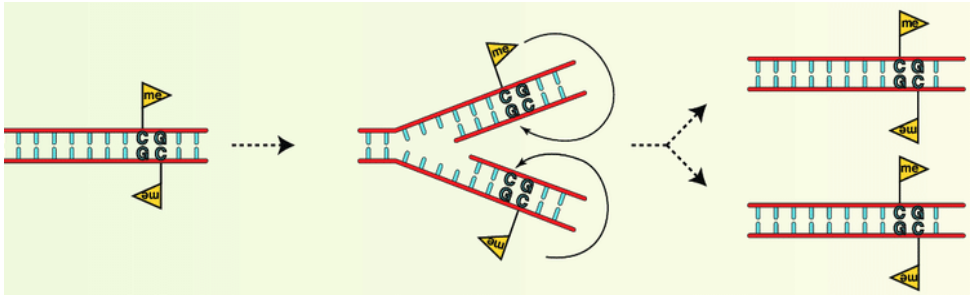
stable? **Environmental influence**

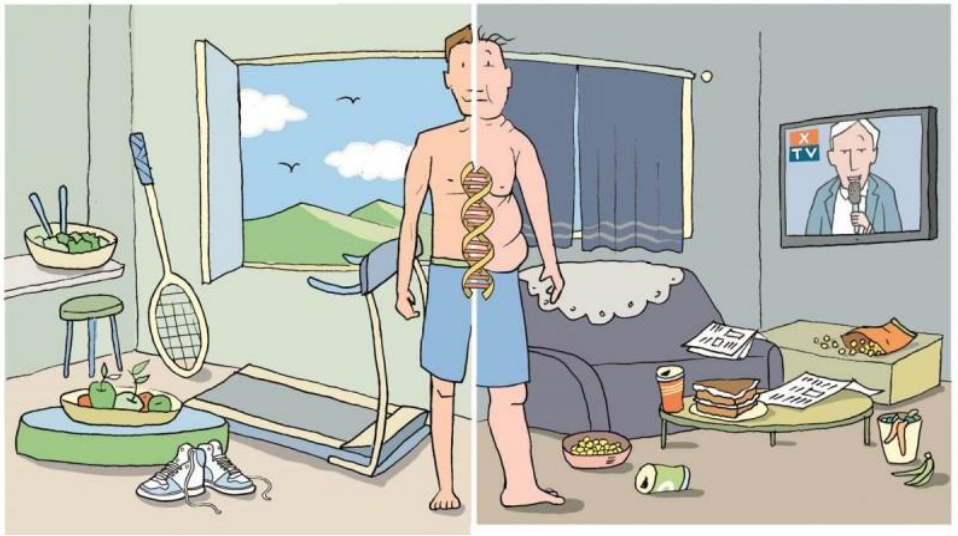
soma and germline

Epigenetic features

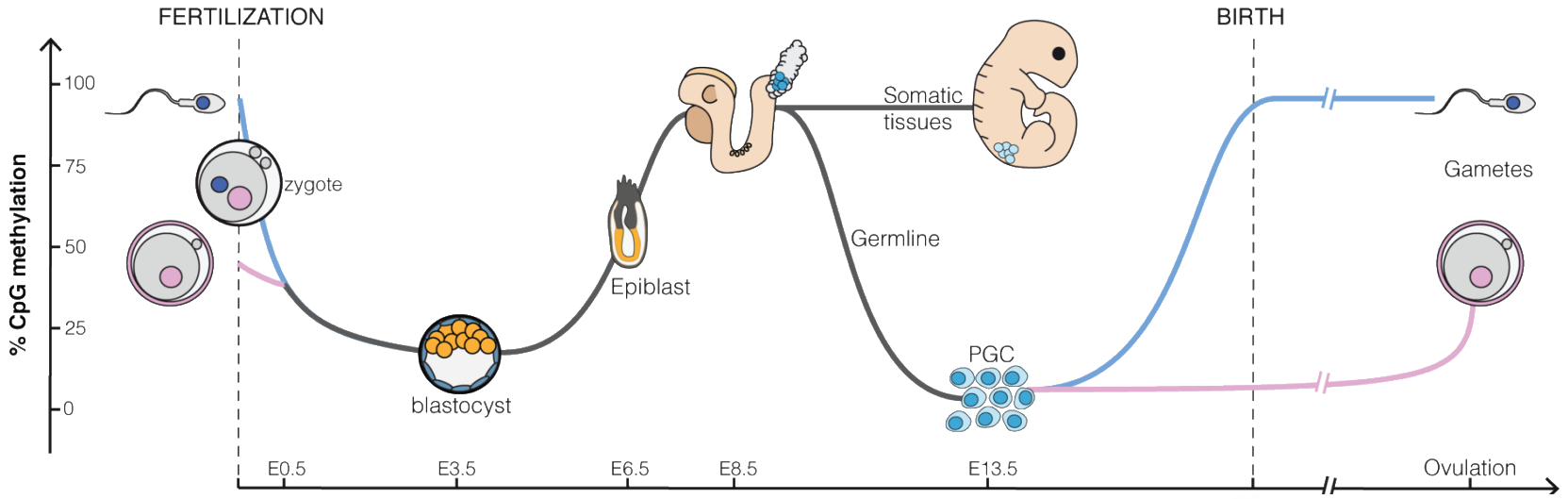
- Gene expression switch: ON/OFF
- Epigenetic markers transmitted during DNA replication/cell division
- Can be influenced by many factors eg. age, stress, environment, diets, toxic chemicals, life style etc.
- Erasable
  - Embryonic development
  - Germline specification



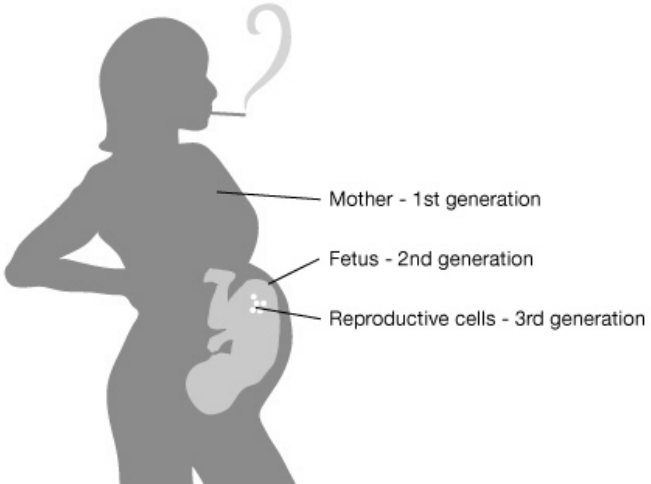




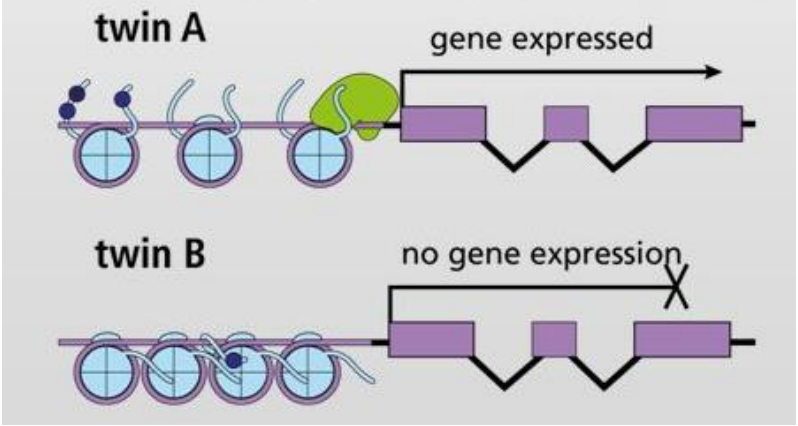
DNA methylation reprogramming

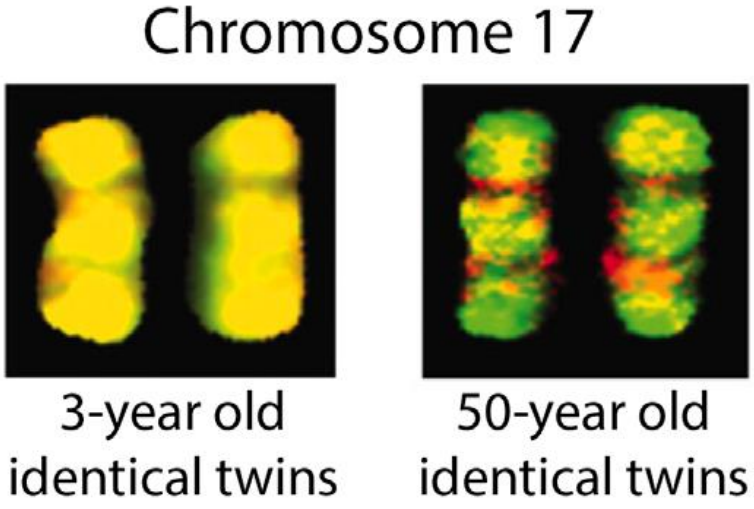


- Happens in cycles
- Erased and re-set in the embryo and gonads
- Multi-generational effects



Epigenetic phenomenon





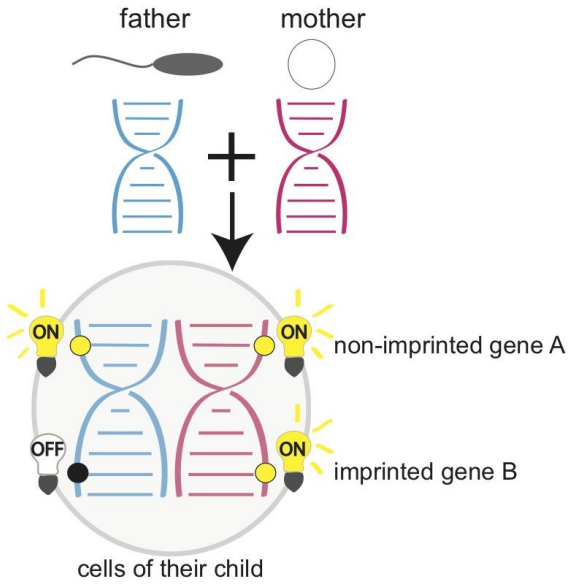
- Yellow indicates shared epigenetic markers
- Environmental influence
- Epigenome of twins has diverged

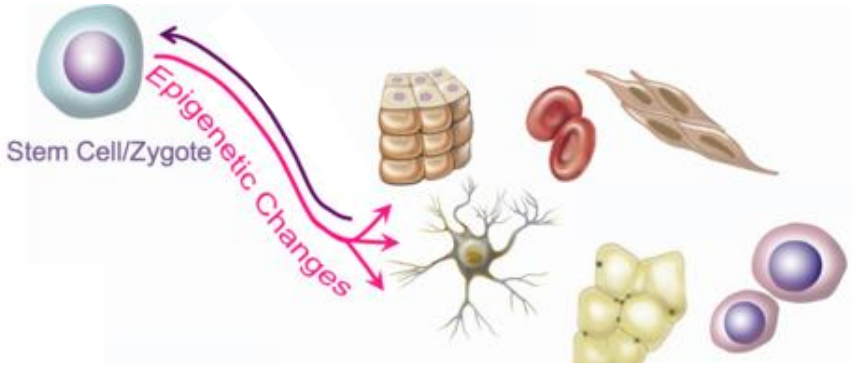
- Different hair colors
- Diseases are not the same in identical twins

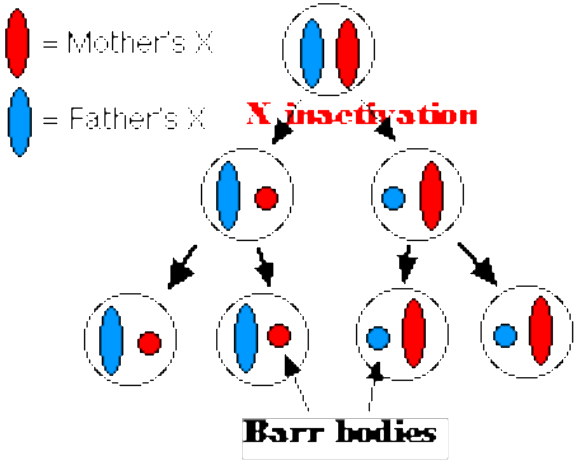
Fraga et al., 2005, PNAS

Epigenetic processes

- Genomic imprinting
- X chromosome inactivation
- Cell differentiation
- Cancer formation







Genomic imprinting

What is imprinting?

- Behavior definition
- A type of learning limited to a sensitive period of an animal's life, generally irreversible
- Recognition of parents immediately after hatching
- First studied in birds, Konrad Lorenz (Nobel prize 1973)

Figure 51.9 Imprinting: Konrad Lorenz with imprinted geese

Behavioral Imprinting

Examples of genomic imprinting in animal science

Donkey

Horse

Mule

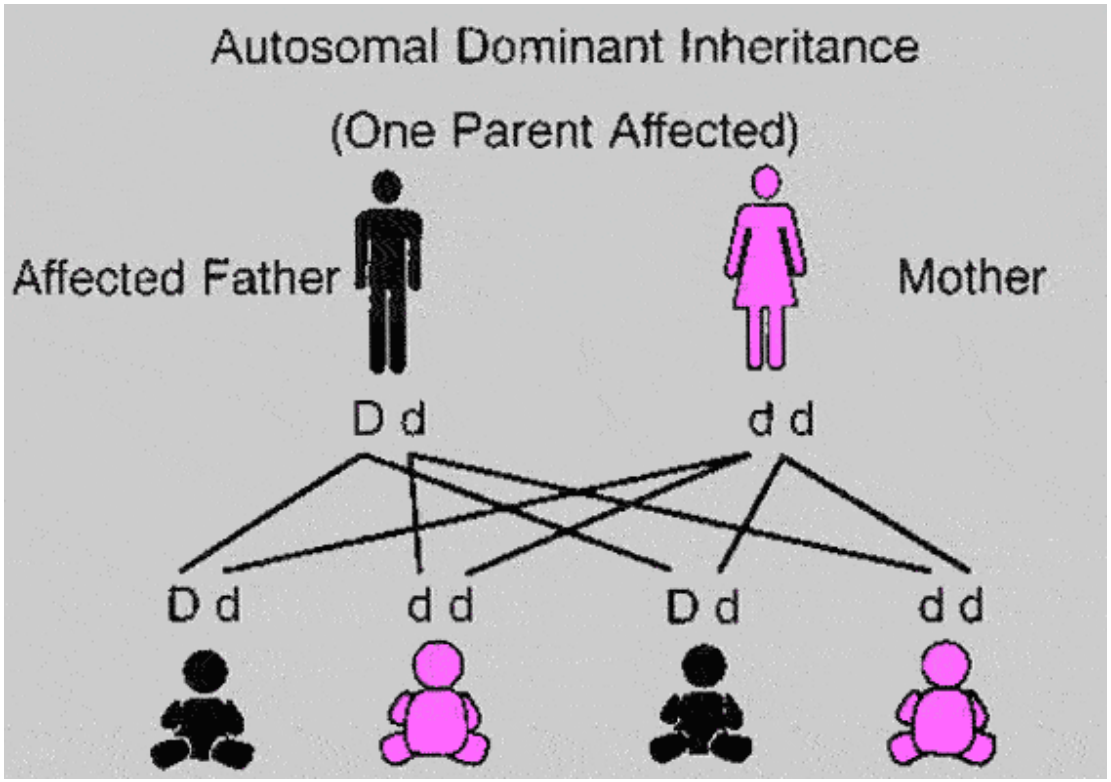
Horse X Donkey

Hinny

Donkey X Horse

- Parental specific effect: size, coat, strength, etc

Mendelian dominant inheritance



Inheritance pattern of genomic imprinting

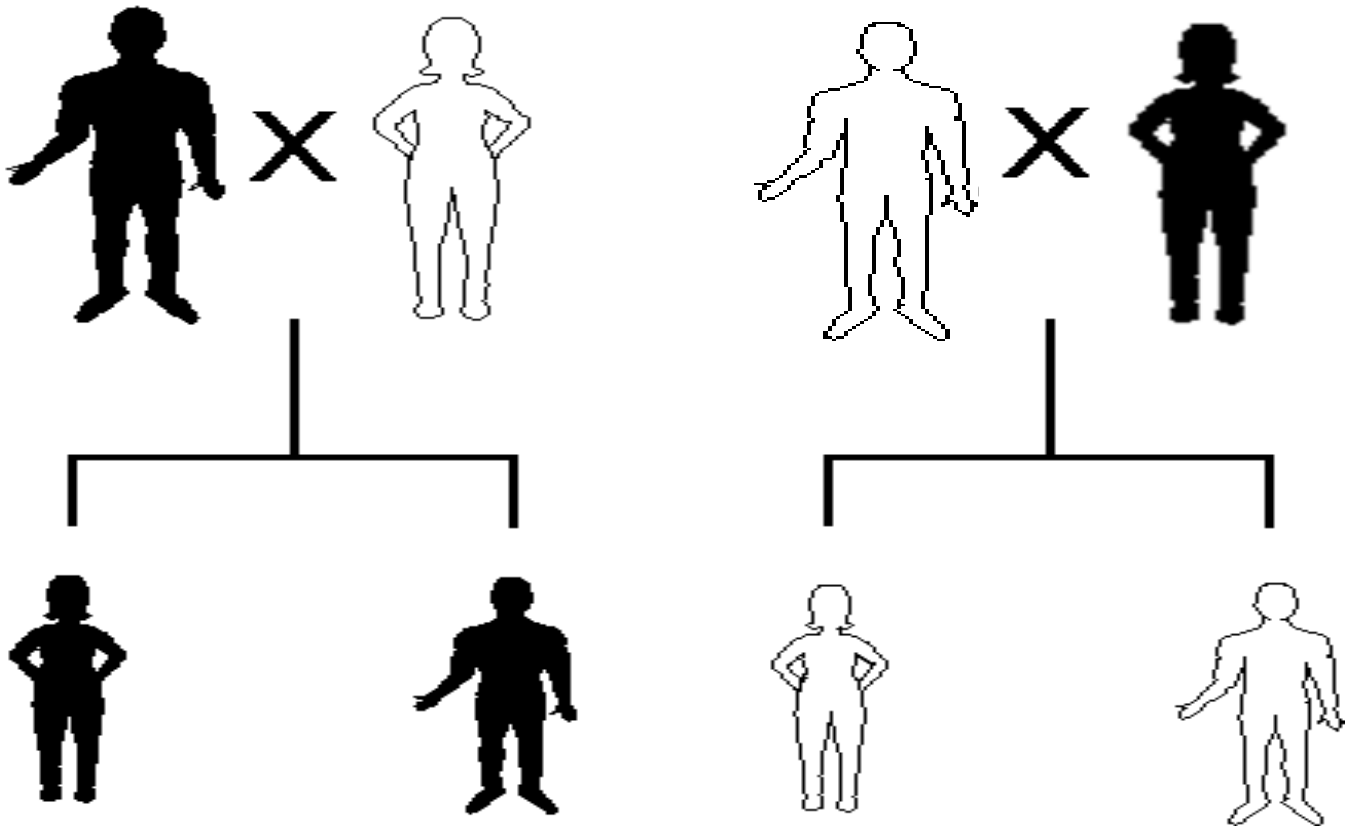
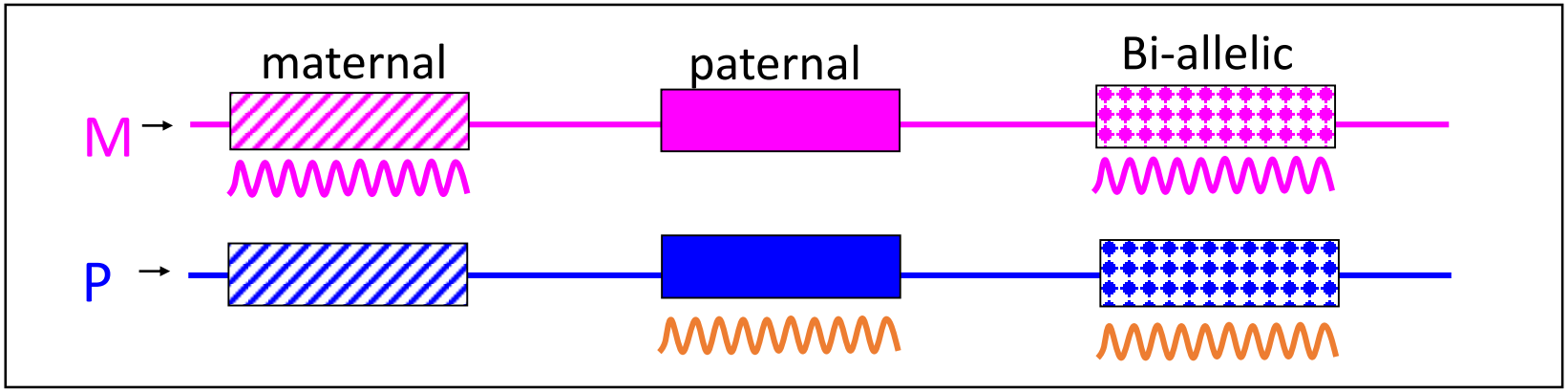


Figure 1: Hypothetical imprinted gene responsible for body color. LEFT: the pigment gene is paternally expressed. Matings between a male who possesses the allele for pigment and a female who possesses the allele for no pigment produces offspring that show only the pigmented phenotype. RIGHT: the pigment gene is not inherited from the father and offspring do not show the pigmented phenotype.

Genomic Imprinting

In mammals, it describes the establishment, maintenance, and downstream effects of functional inequalities between a gene's two parental alleles

What is genomic imprinting?



Imprinted = inhibited

- DNA methylation
- Histone modification
- Non-coding RNA

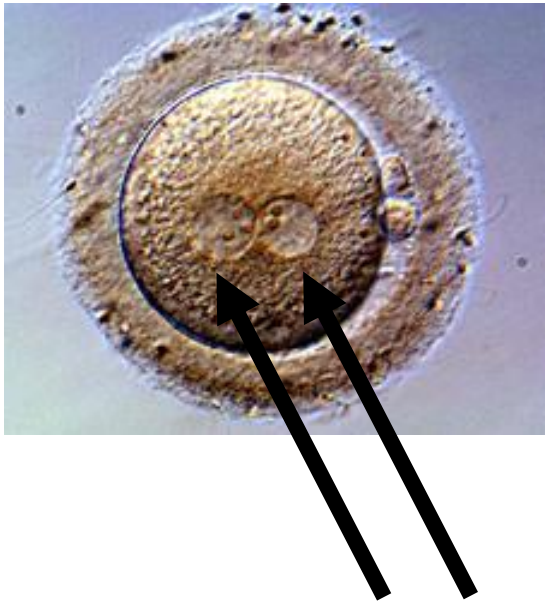
Maternally Imprinted = Paternally Expressed

Paternally Imprinted = Maternally Expressed

How was genomic imprinting studied?

- Sexual reproduction in mammals
- Parental specific effects in development suspected
- A Surani (UK), D Solter (Germany) 1980s
- Nuclear transplantation experiment:
  - Gynogenetic embryos: “big” fetus, small placenta
  - Androgenetic embryos: “big” placenta, small fetus
  - Development retardation and fetal death in both cases

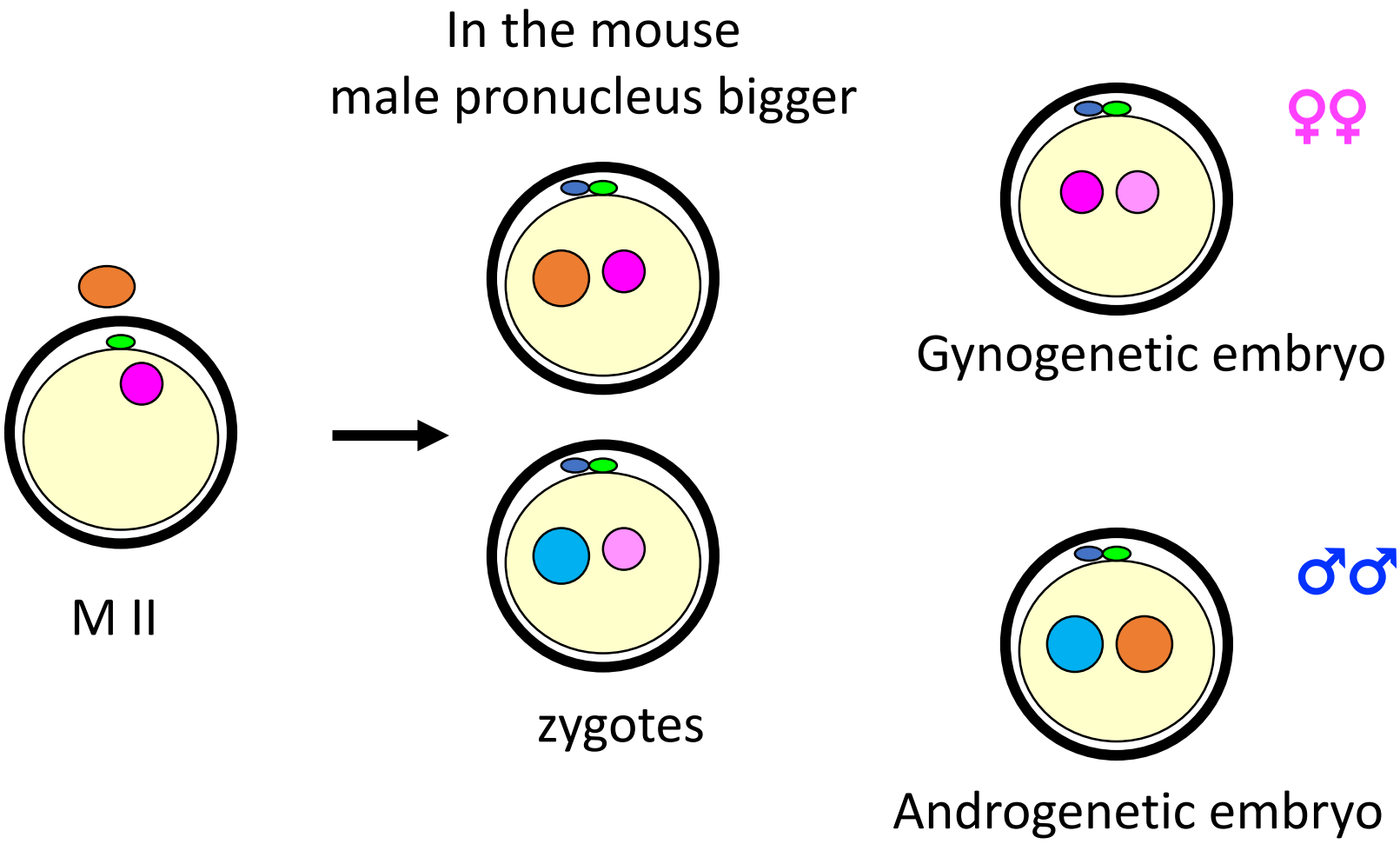
Nuclear transplantation



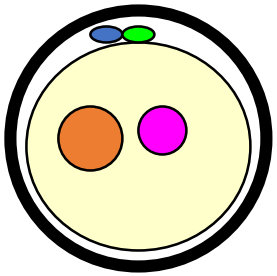
Fertilized egg (zygote)

Male and Female Pronuclei

Nuclear transplantation

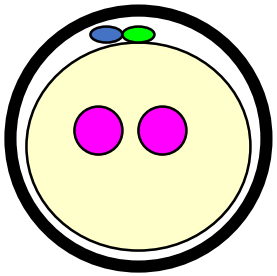


Nuclear Transplantation



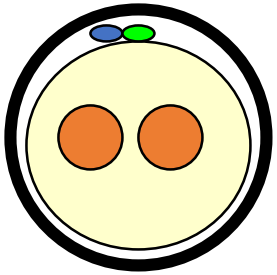
Zygote (♀♂)

Embryo Transfer → Full-term development



Gynogenetic (♀♀) embryo

Embryo Transfer → Placental growth retardation



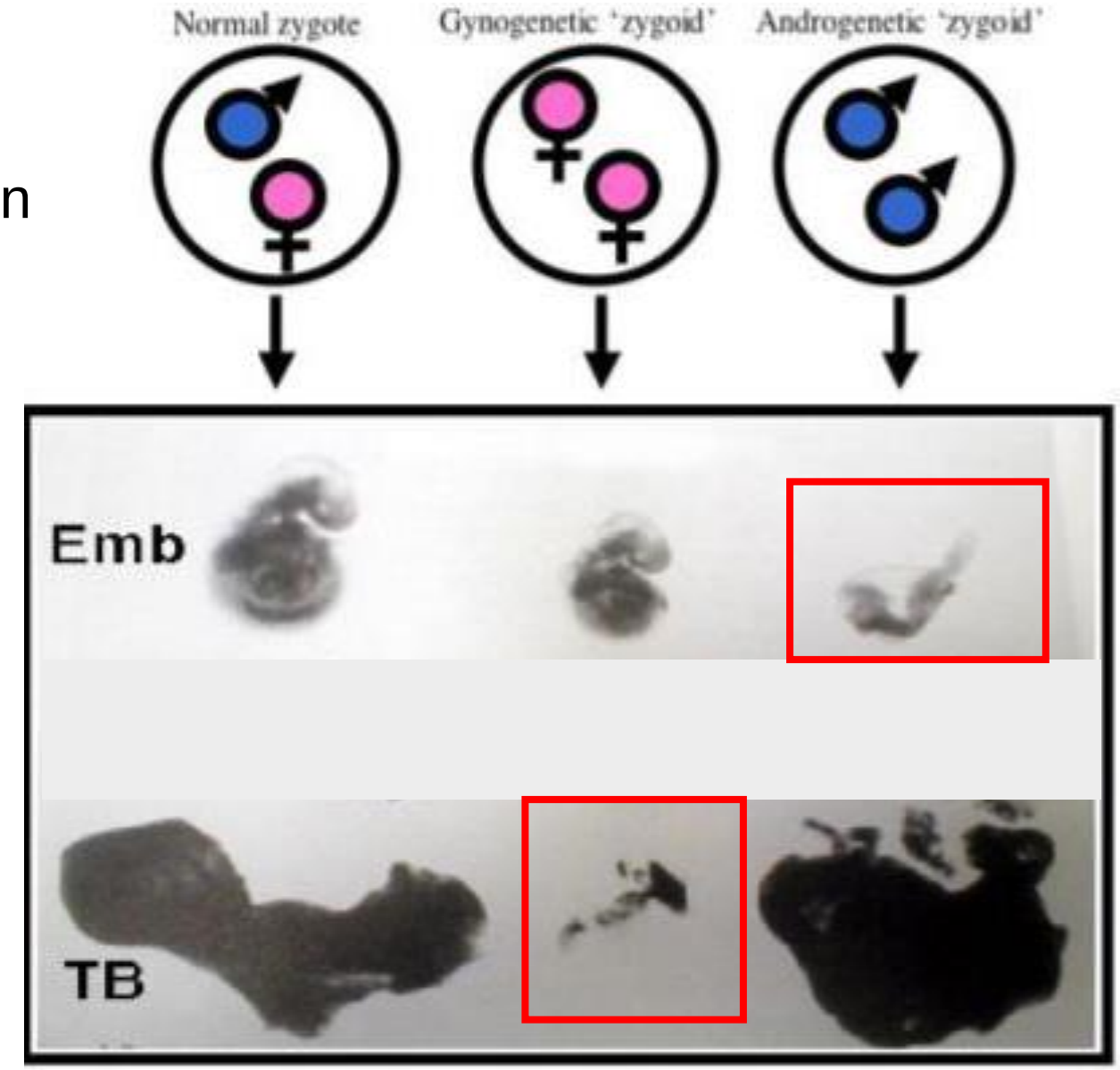
Androgenetic (♂♂) embryo

Embryo Transfer → Fetal growth retardation

Nuclear Transplantation

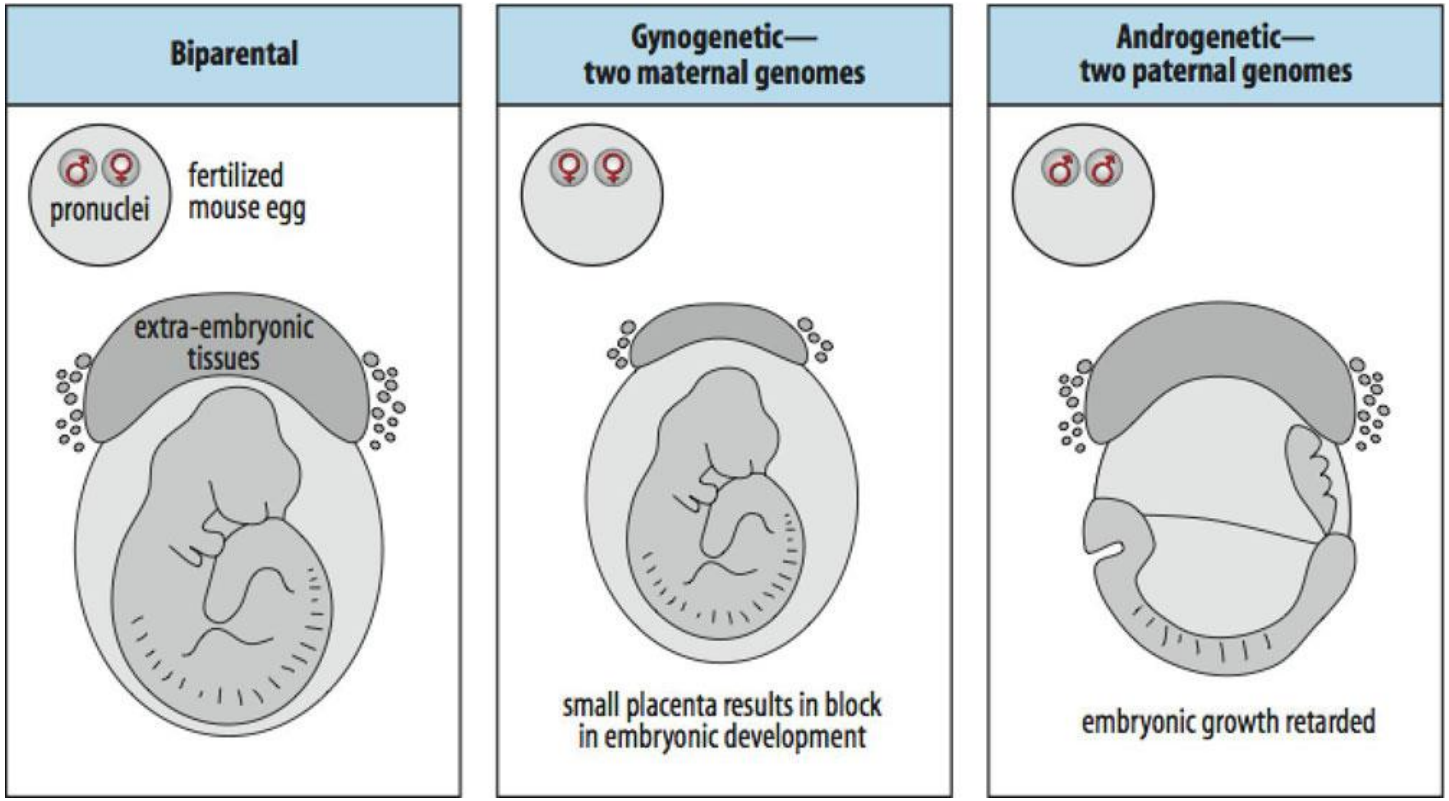
Embryo

Placenta



Surani, McGrath and Solter, 1984-1987

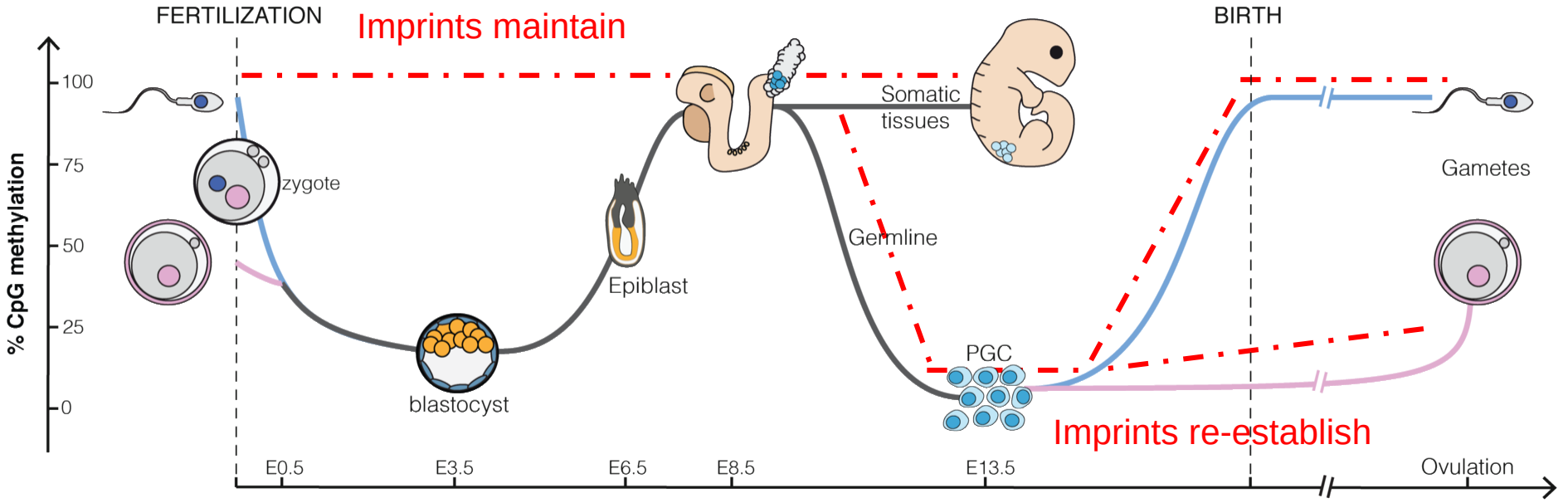
Examples of imprinted genes



Most famous pair of genomic imprinted genes

- Insulin-like growth factor II (*IGF2*), paternally expressed, promotes growth, especially in placenta
- IGF-II receptor (*IGF2R*), maternally expressed, inhibits growth

How is genomic imprinting in life cycles

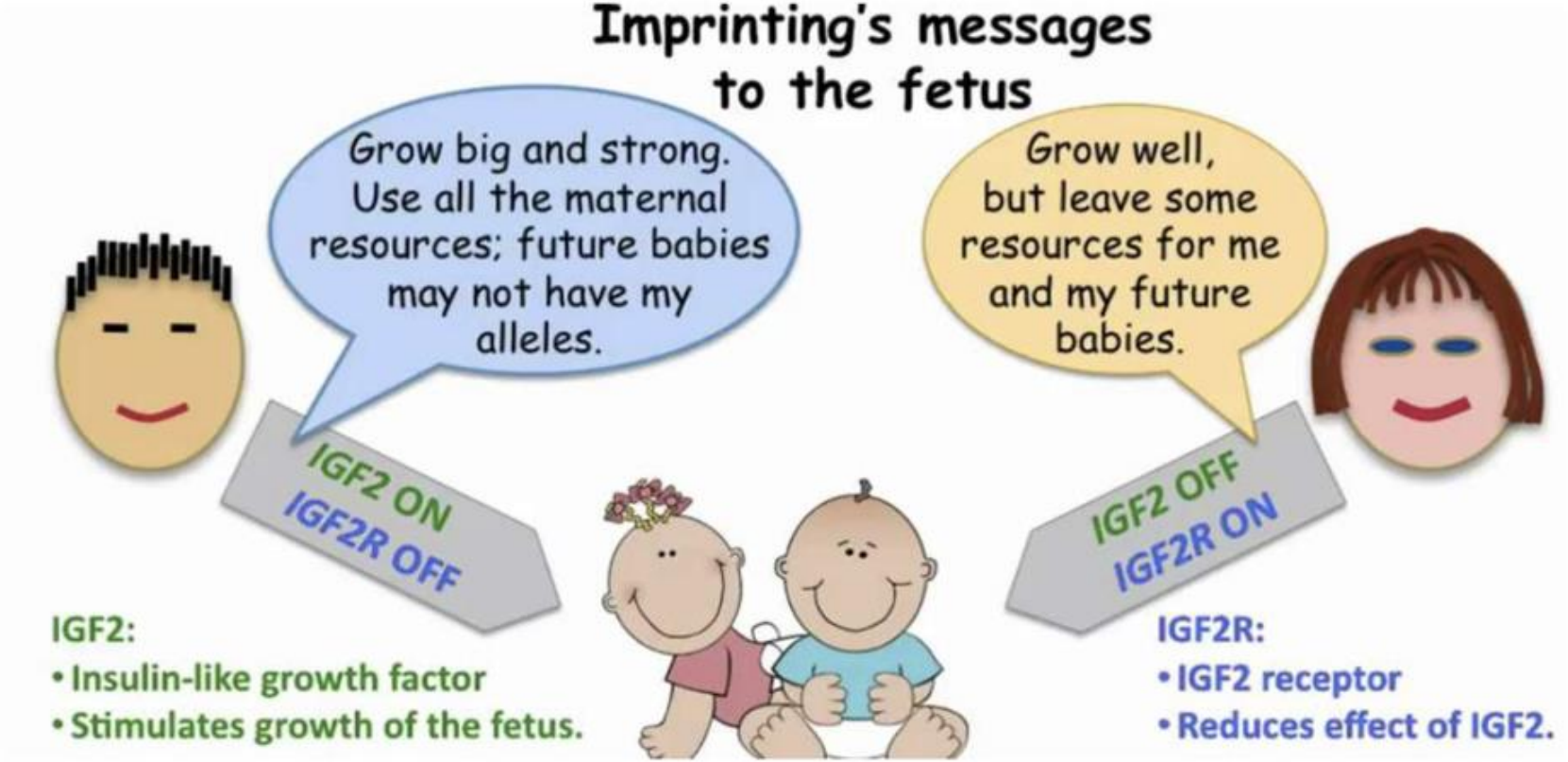


- Somatic cells: maintain parental imprints
- Germ cells: Imprints are erased in the primordial germ cells
- Imprints are re-established on the DNA in male or female gametes for maternal or paternal imprints
- In a new embryo, the imprints are maintained during embryonic development, erased again in the germ cells.

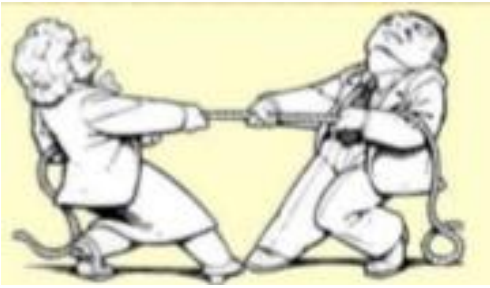
Why imprinting?

- Evolution advantage of imprinting?
  - Undermine the benefit from diploid
- Ensures no asexual reproduction in mammals
  - Gynogenetic/Androgenetic embryos will not develop naturally
- Why imprinting is still with us?
  - Several hypotheses proposed
  - Parental conflict hypothesis

Parental Conflict Theory



Parental Conflict Hypothesis

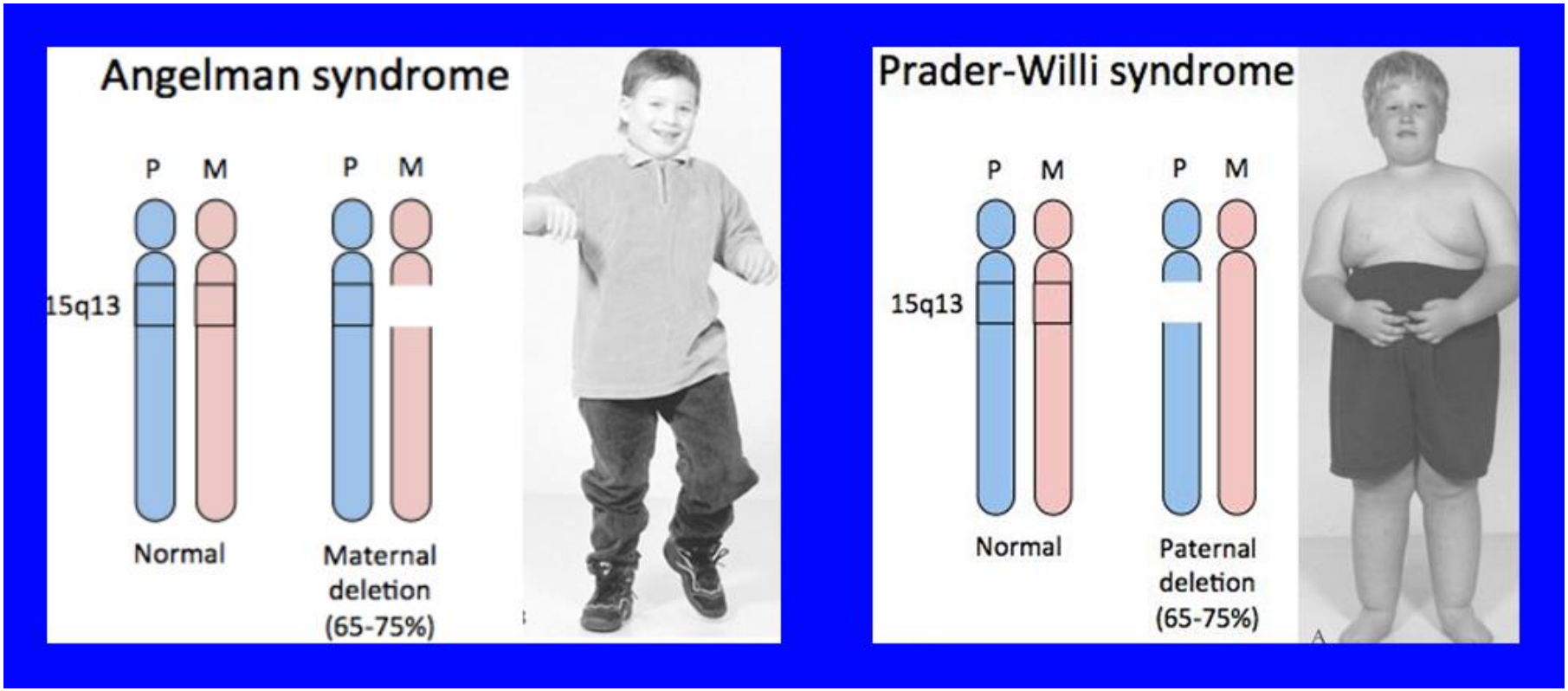


- Conflicts at the placenta (maternal-fetal interface)
- Father wants to increase the survival of his offspring: promote placenta/fetal growth.
- Mother wants to promote the survival of all her offspring (including subsequent pregnancies) and preserve herself: inhibit placenta/fetal growth.
- Most imprinted genes regulate fetal and post-natal growth, many are only imprinted during fetal development or only in the placenta

Imprinting diseases

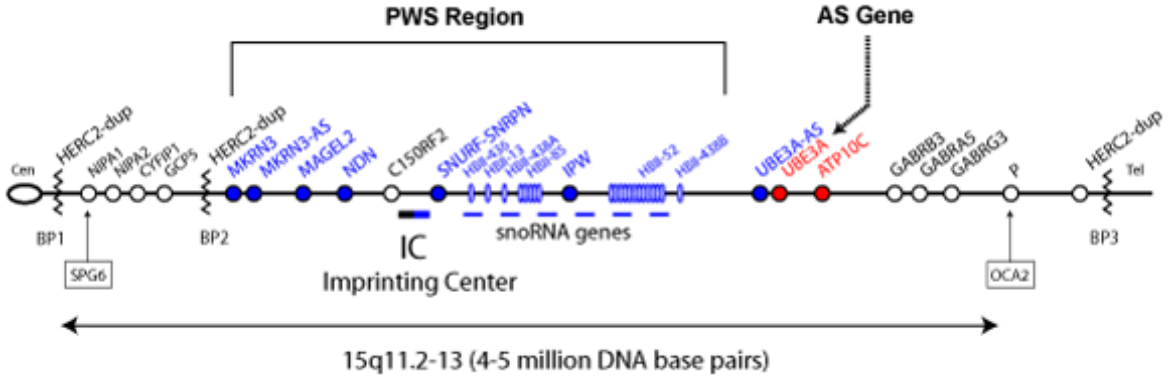
Deletion on the long arm of chromosome 15 (q13)

- If deletion in maternal allele: Angelman syndrome
- If deletion in paternal allele: Prader-Willi syndrome



Developmental disability; intellectual disability

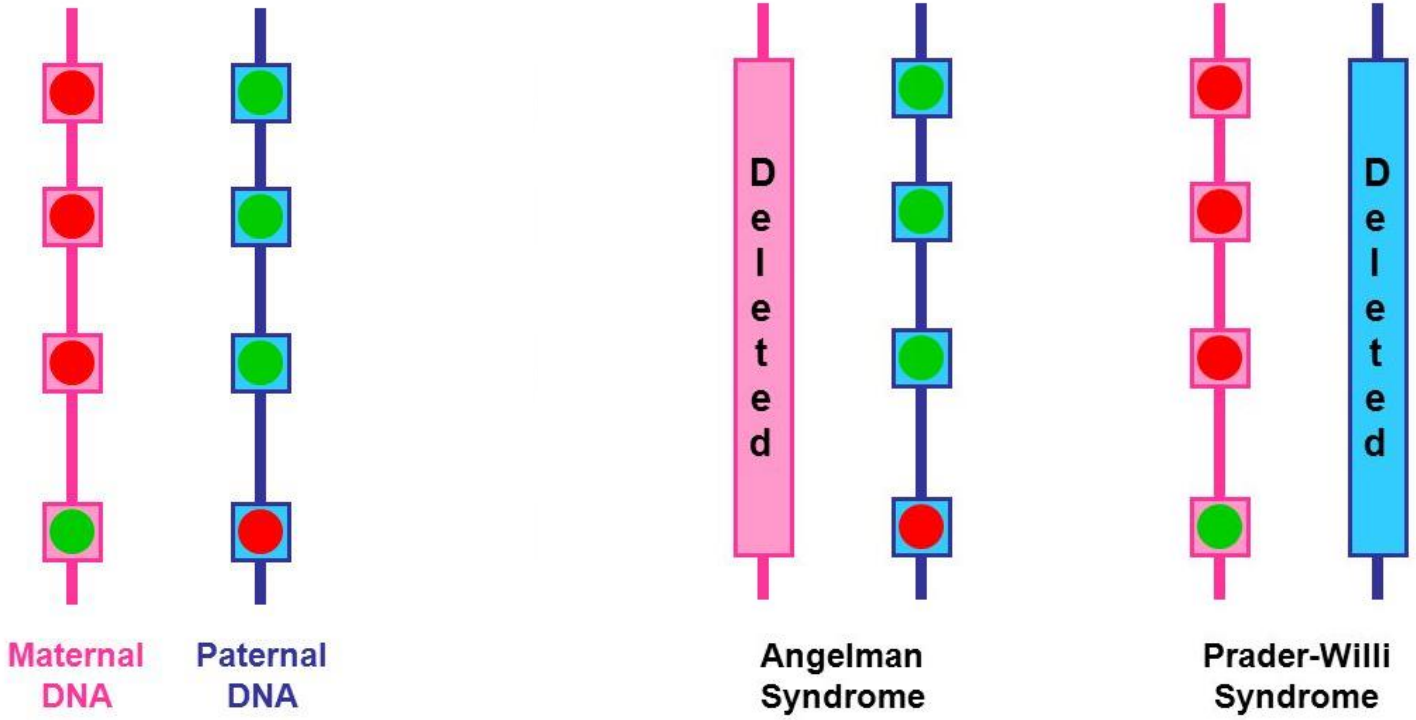
Growth retardation; excessive hunger; obesity



Blue: paternally expressed
Red: maternally expressed
Black: bi-allelically expressed

Gene imprinted (turned off)

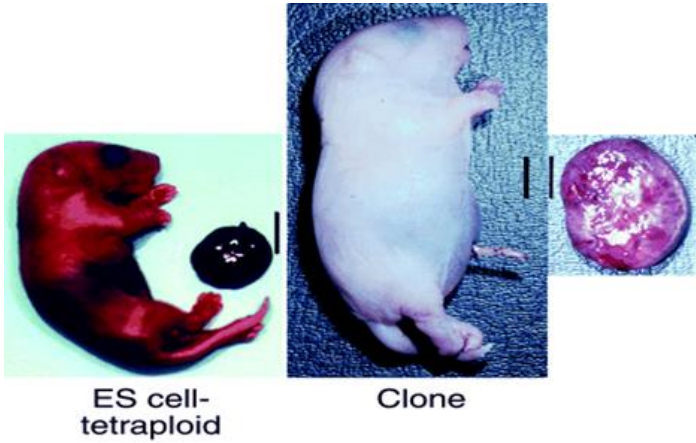
Gene not imprinted (turned on)



Beckwith-Wiedemann syndrome (overgrowth disorder)

- Large newborn (large for gestational age)
- Large placenta
- Large tongue, sometimes protruding
- Large prominent eyes
- Creases in ear lobes
- Abdominal wall defect: umbilical hernia
- Separated abdominal muscles (diastasis recti)
- Undescended testicles (cryptorchidism)
- Low blood sugar (hypoglycemia)
- Lethargy (lots of sleep)
- Seizures
- Enlargement of some organs and tissues

Imprinting and embryo biotechnology



- Human IVF
  - Beckwith-Wiedemann syndrome
- Embryo culture effect (large offspring syndrome):
  - overweight at birth, reluctant to suckle, difficulty breathing and standing, hypothermia, large placenta, death (slow suffocation)
- Mono-allelic expression maintained during early embryo development, sub-optimal culture conditions can affect this

Summary of genomic imprinting

- Examples of genomic imprinting
- Genomic imprinting definition
- Nuclear transplantation experiments
- Parental conflict hypothesis
- Life cycle of genomic imprints
- Imprinting diseases

Questions

Genomic imprinting refers to the fact that

https://www.polleverywhere.com/multiple_choice_polls/GxDR66QbokvdNEg

A. Some proteins are made from mRNA transcribed by the mother.

B. One cell type follows the developmental path of another.

C. New born birds recognition of parents immediately after hatching.

D. Gene activity depends upon whether the gene is of maternal or paternal origin.

Questions

When the specific imprinted gene region from the chromosome 15 of the mother's missing it leads

https://www.polleverywhere.com/multiple_choice_polls/PNQaY3MxCKXGv9s

A. Pader Willi syndrome

B. Angelman syndrome

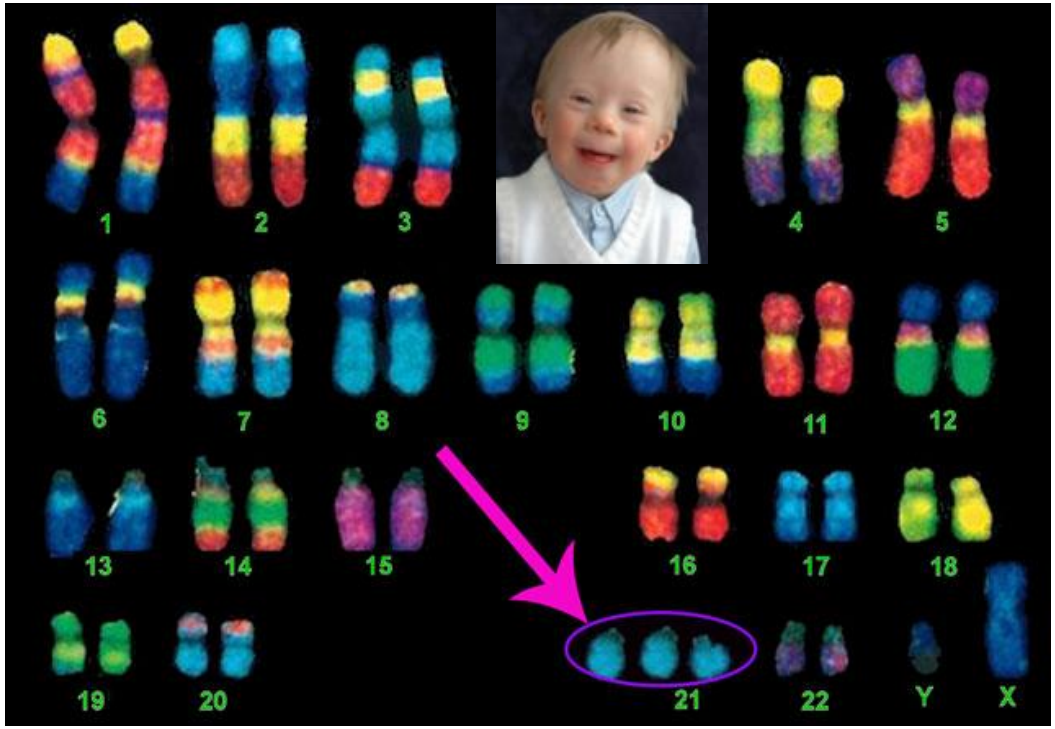
C. Down's syndrome

D. Beckwith-Wiedemann syndrome

X Chromosome Inactivation (XCI)

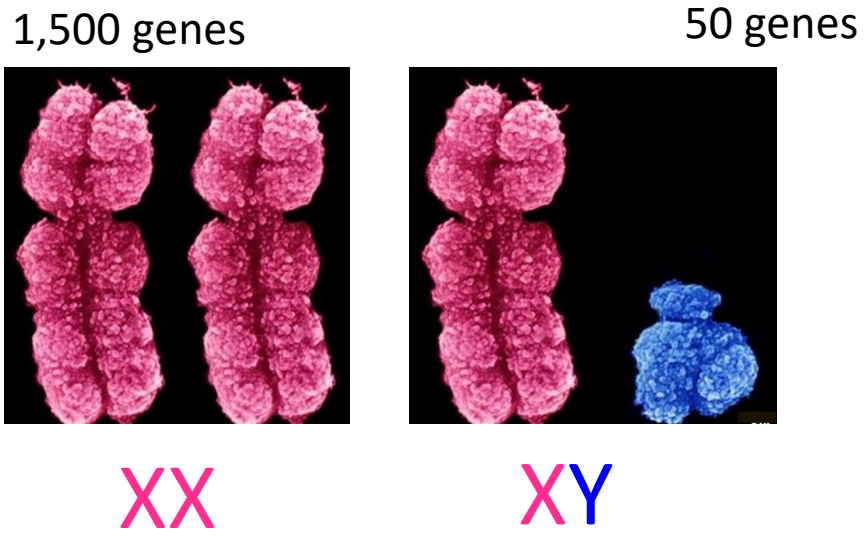
Gene dosage

- Diploid is essential
- Genetic diversity and masks recessive mutated gene
- Deviations from 2N can be lethal
- Chromosome 21: smallest, few genes
  - Down's syndrome
- Trisomy of other chromosomes: partial and or mosaic
- Incompatible with life

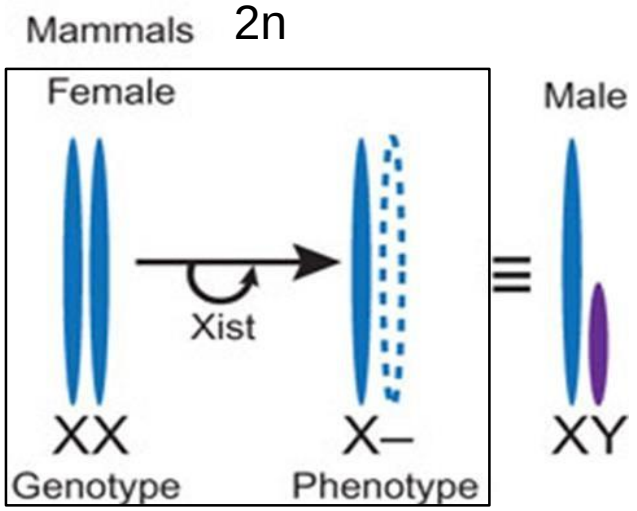


Gene dosage problem in sex chromosomes?

- Both derived from autosomes
- Specialized in sex determination
- Different in
  - Size
  - Function
  - Gene content



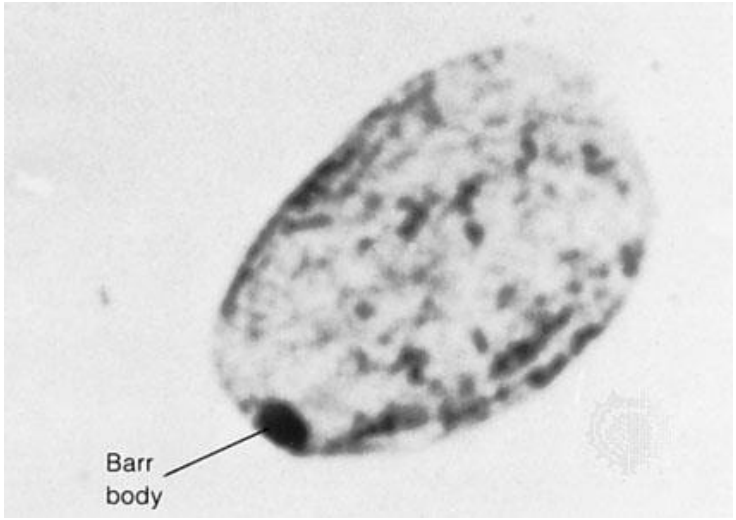
X chromosome inactivation

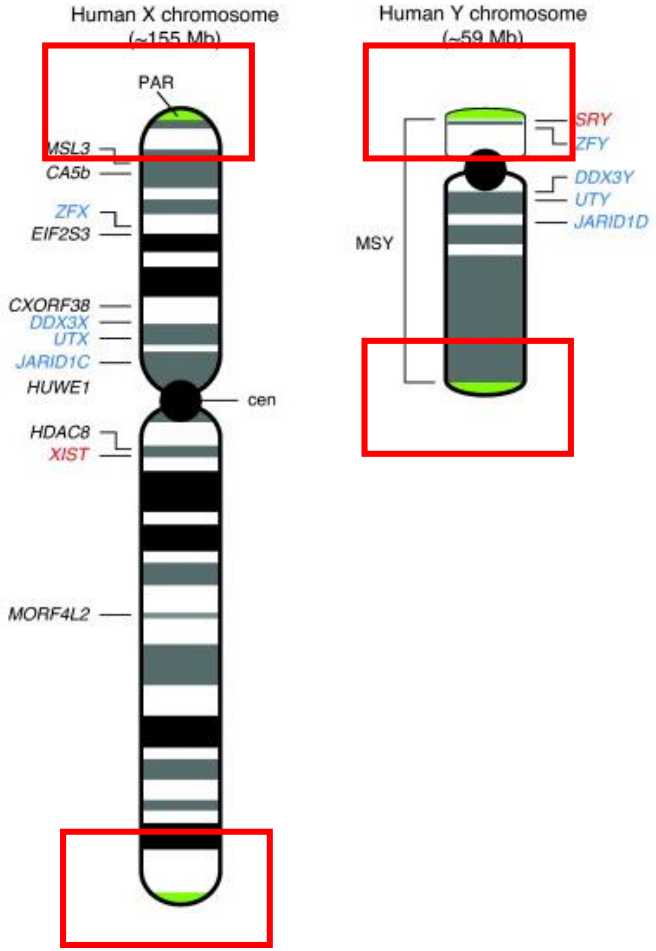


For every 2n, one active X (Xa)

XCI in mammals

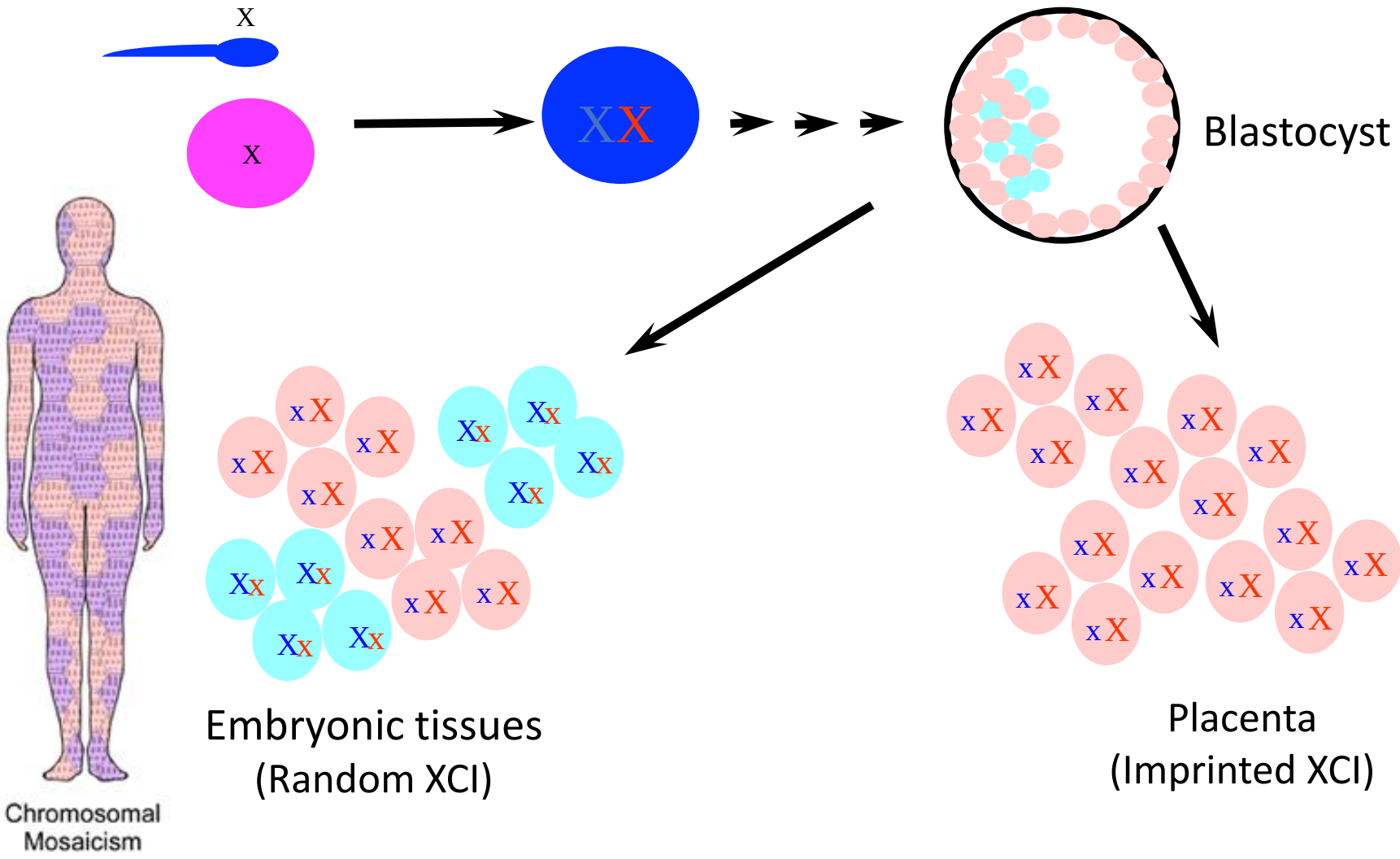
The Barr body = the inactivated X (Xi) condensed heterochromatin





- XCI escapee: 5-15% of X-linked genes escape XCI in female, pseudoautosomal region (PAR)

Random and imprinted X-inactivation



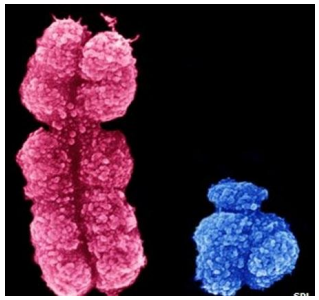
How does the single X balance with AA?

XX

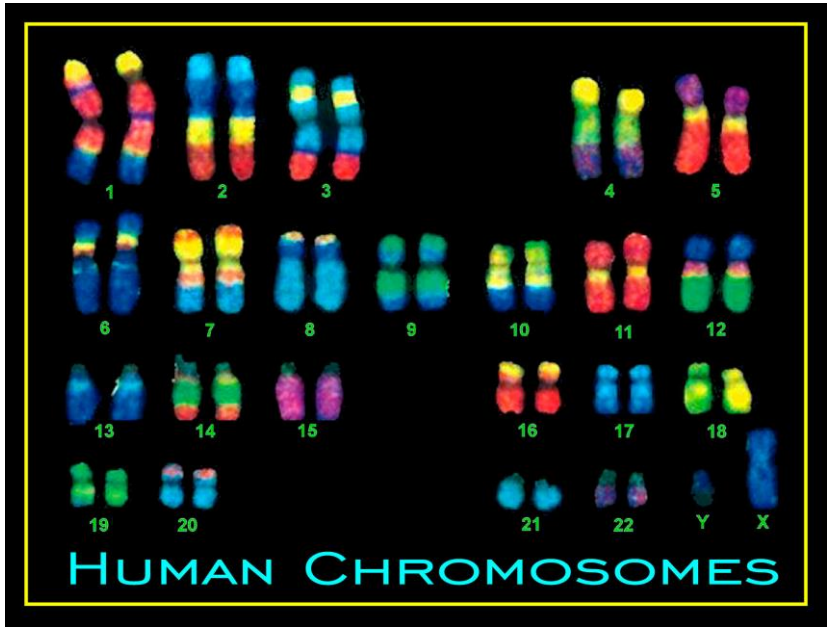
XCI

Xx_i

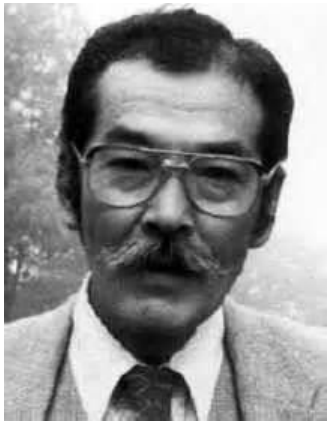
Dosage compensation



XY



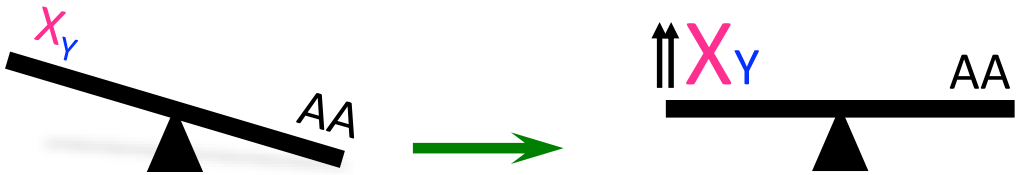
X : AA?



Susumu Ohno

Ohno's Hypothesis: X chromosome dosage compensation in mammals

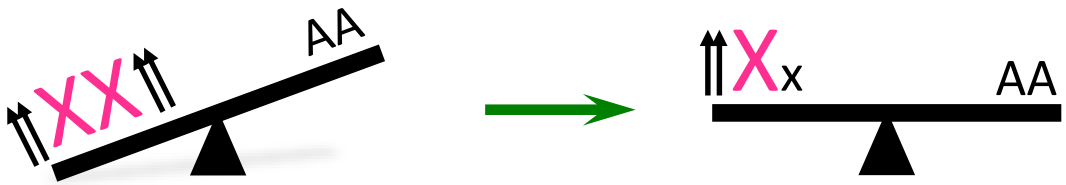
Male



1 : 2

2 : 2

Female



4 : 2

2 : 2

Mechanisms of X-inactivation

Counting

Initiation

Spreading

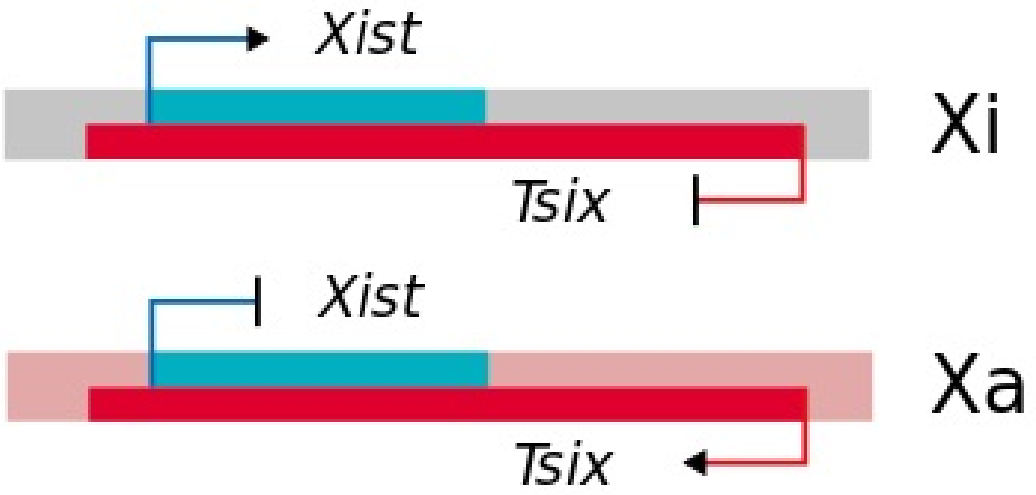
Maintenance

Counting X chromosomes

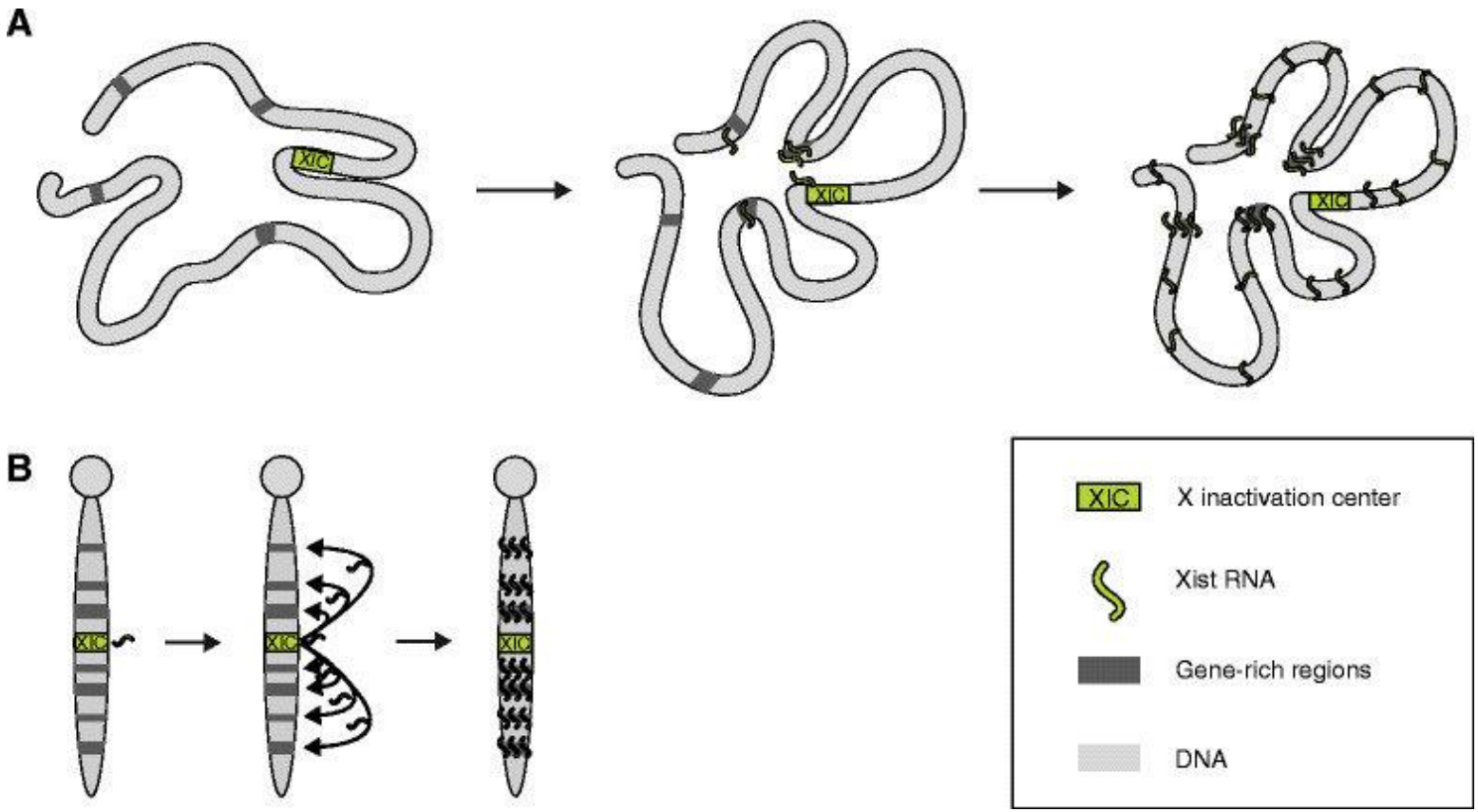
Karyotype	Sex	Xi number
46 (2N), XY	Male	0
46 (2N), XX	Female	1
45, XO (Turners)	Female	0
47, XXY (Klinefelter's)	Male	1
48, XXXY (Klinefelter's)	Male	?
47, XXX (super female)	Female	?
48, XXXX (super female)	Female	?
4N, XXXX cells		?
4N, XXYY cells		?

Initiation: The *Xist* Gene

- *X-inactivation specific transcript (XIST)*
- *Xist* is a switch for X inactivation.
- Located in the X inactivation center (XIC)
- Transcribed only from the inactive X (one of XCI escapees)
- Methylated on active X in male and female

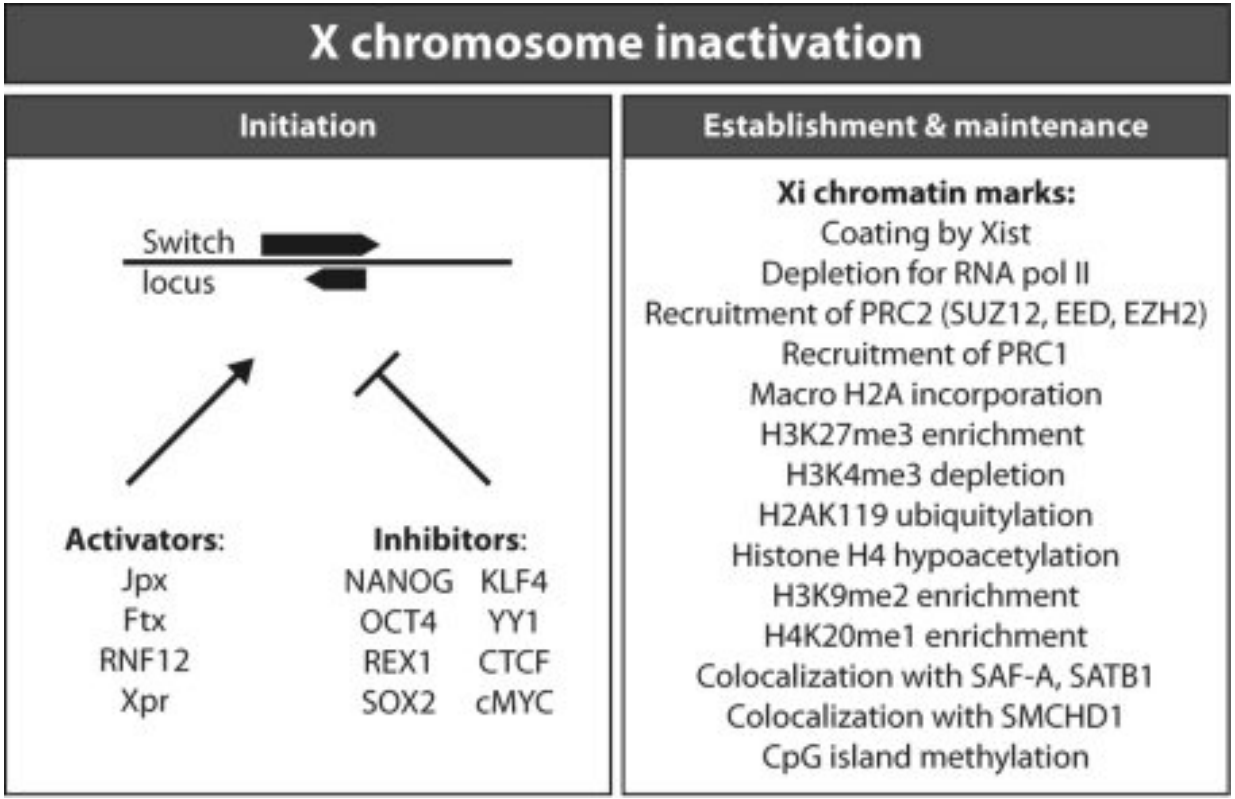


Spreading:



Cerase et al., 2015 Genome Biol

Maintenance of inactive state of Xi:



- Maintained by numbers of histone modifications, protein complexes, and noncoding RNA for the Xi
- Maintained through cell divisions

Questions

Dosage compensation of X-linked genes in mammals is achieved by

https://www.polleverywhere.com/multiple_choice_polls/3I2o3gEhDTiQ7Zc

A. Forming genetic mosaics in females with cells with one functional X-chromosome and double the X outputs.

B. A gene that is turned off on Y-chromosome in males that allows expression of the X-chromosome.

C. A site on a chromosome which controls X-expression called the X-hyperactivation center.

D. Both X-chromosomes in the female being inactivated.

Questions

Which of the following doesn't agree with XIST

https://www.polleverywhere.com/multiple_choice_polls/3bm6vsa58rm5iE5

A. It codes for a non-coding RNA that coats the inactive X chromosome into a barr body

B. It is the only active gene in inactive X chromosome

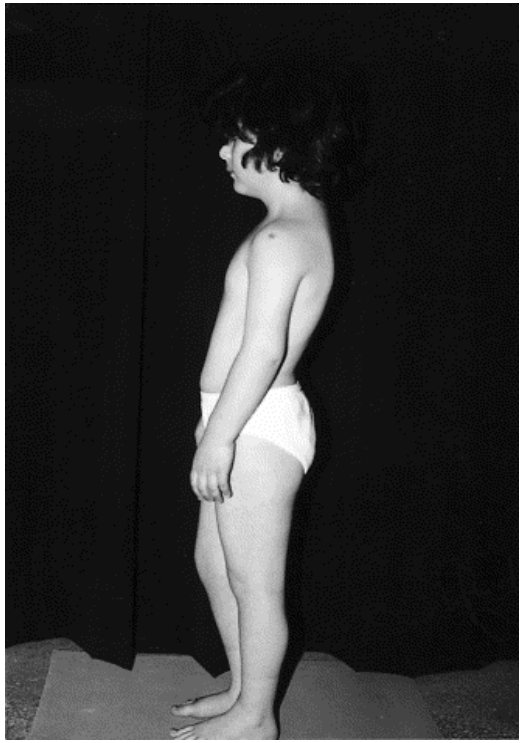
C. Inactivation is seen in female somatic cells

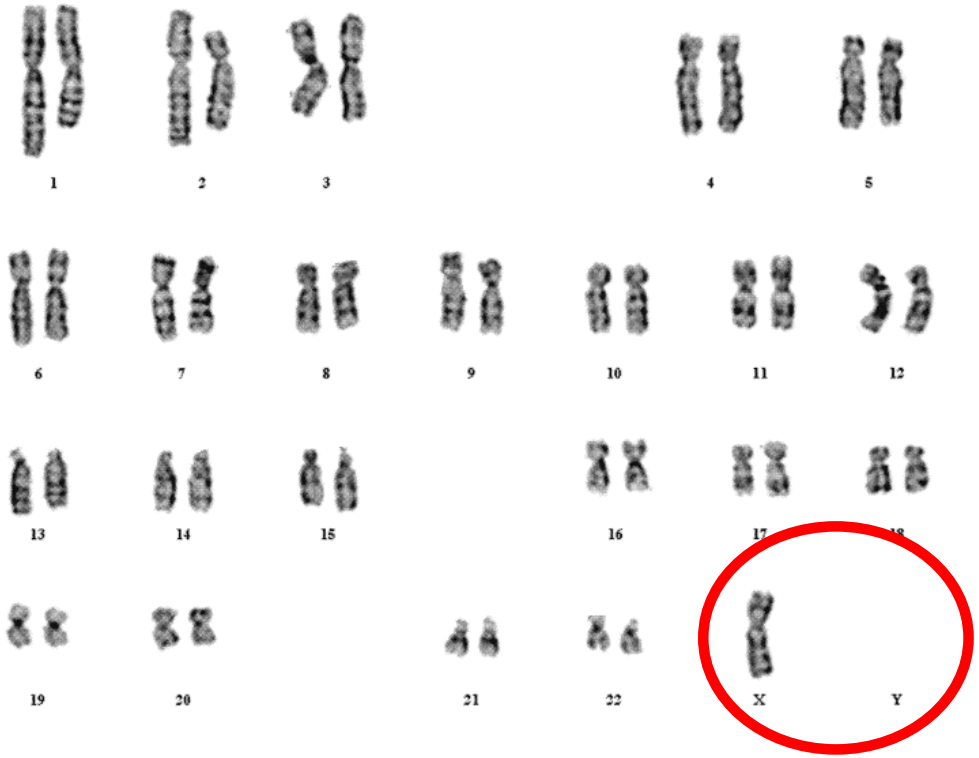
D. XIST gene on the active X chromosome of males and females is typically methylated

Genetic diseases associated with abnormal sex chromosomes

- Turner’s syndrome (45/X,0)
- Klinefelter's syndrome (47/XX,Y)

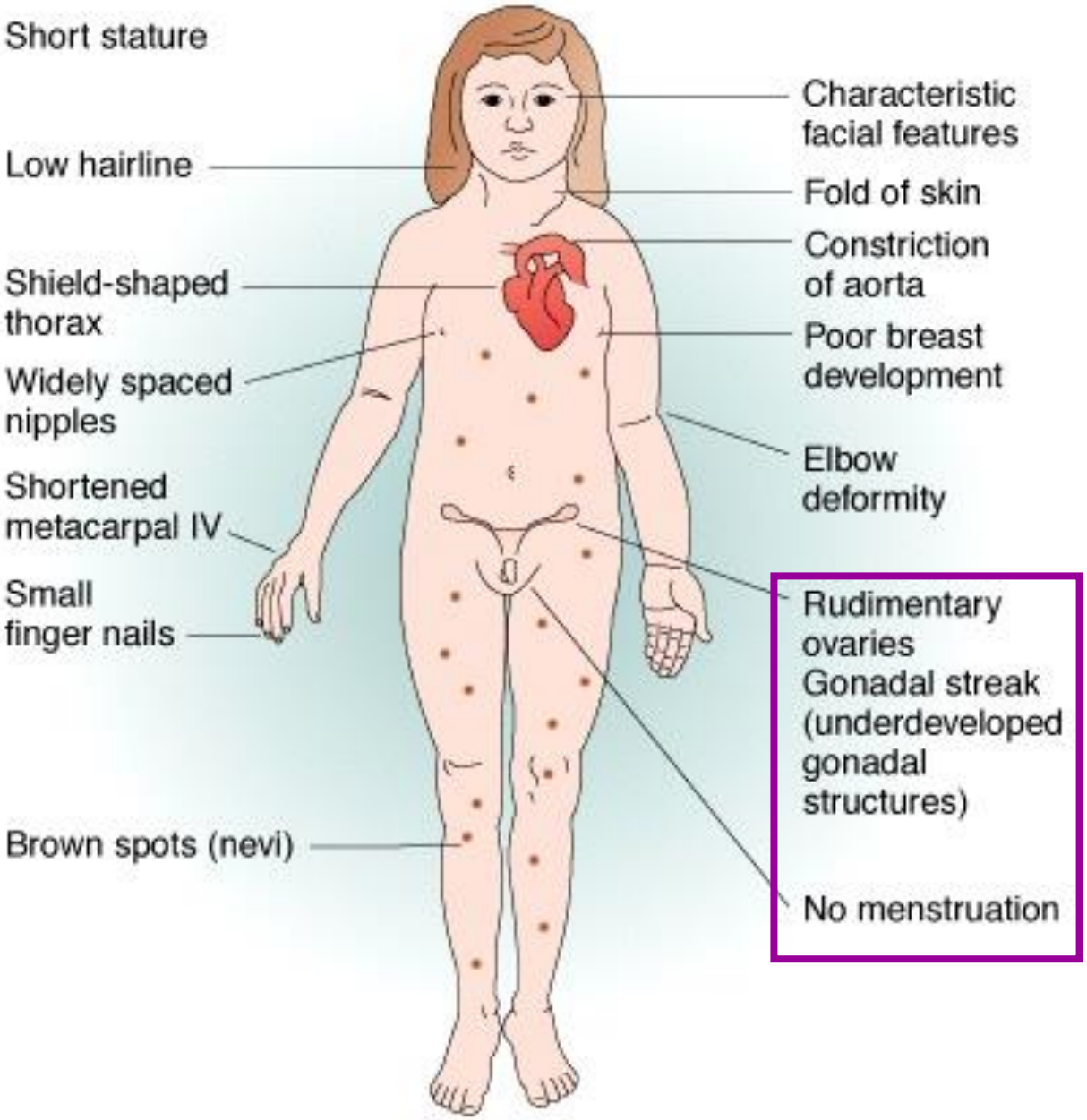
A Turner's patient with a 45, X karyotype

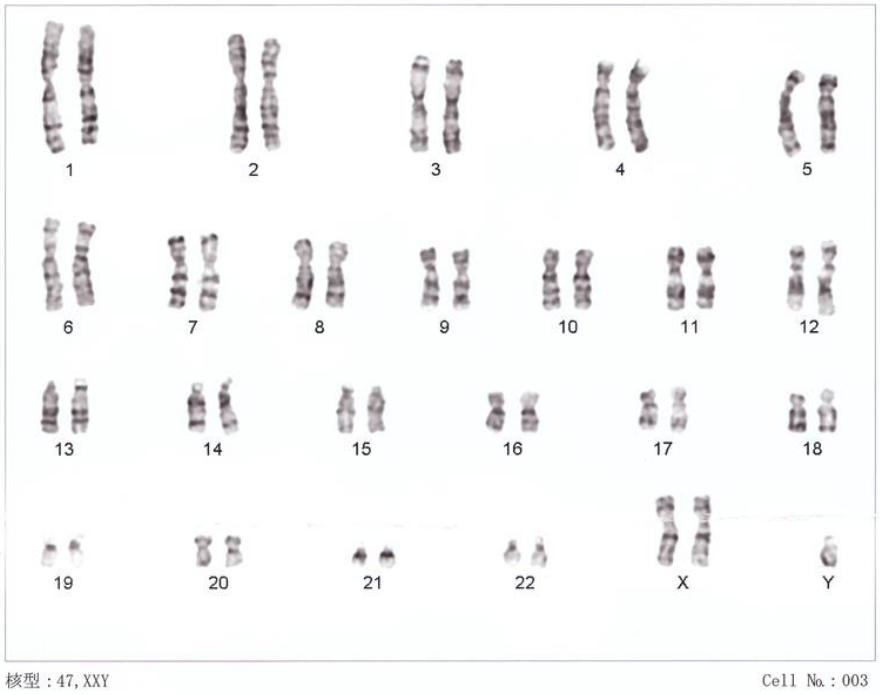


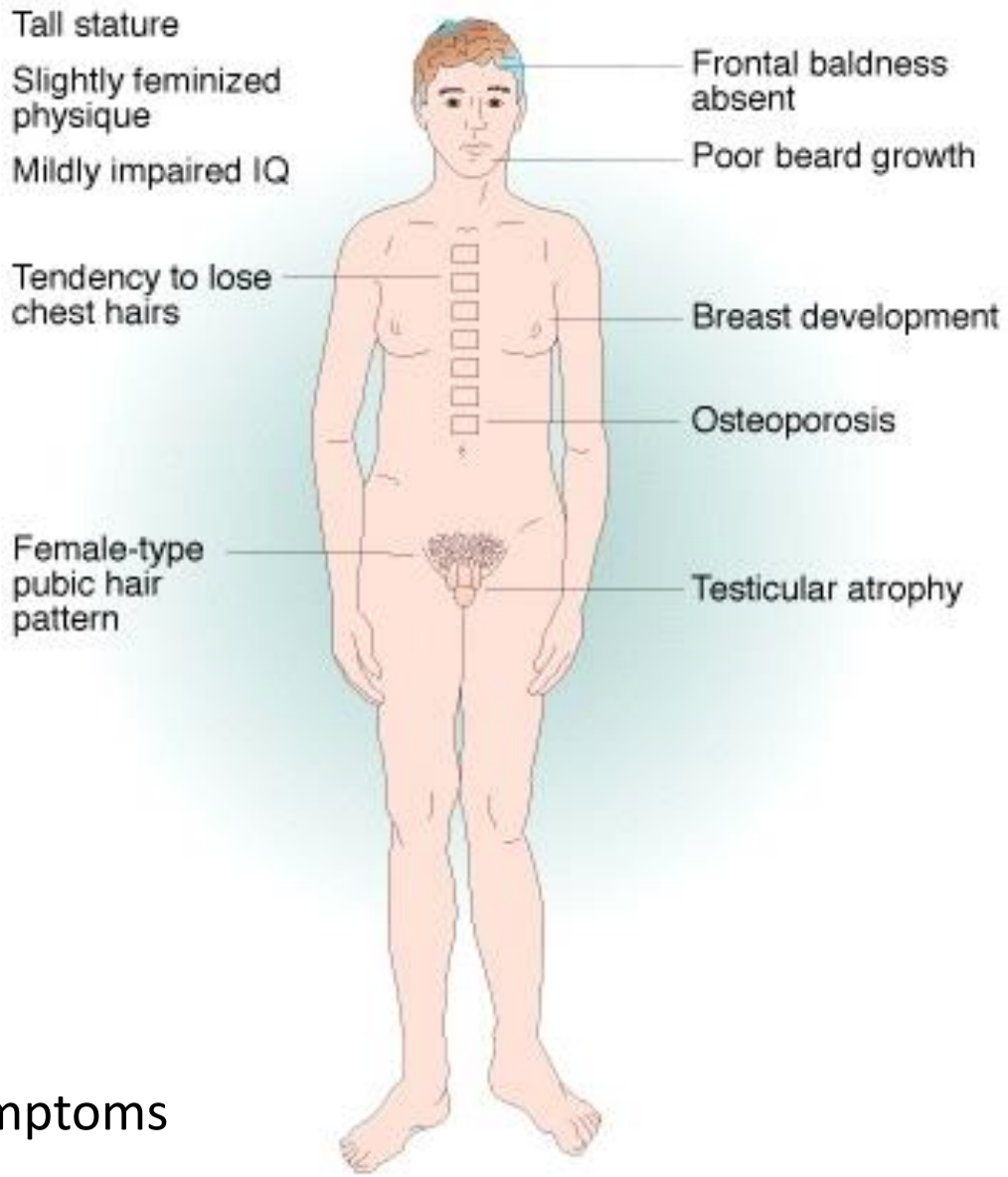


Ozkul et al., Ann. Genet. 2002; 45:181-3.

1 in 2,500 girls





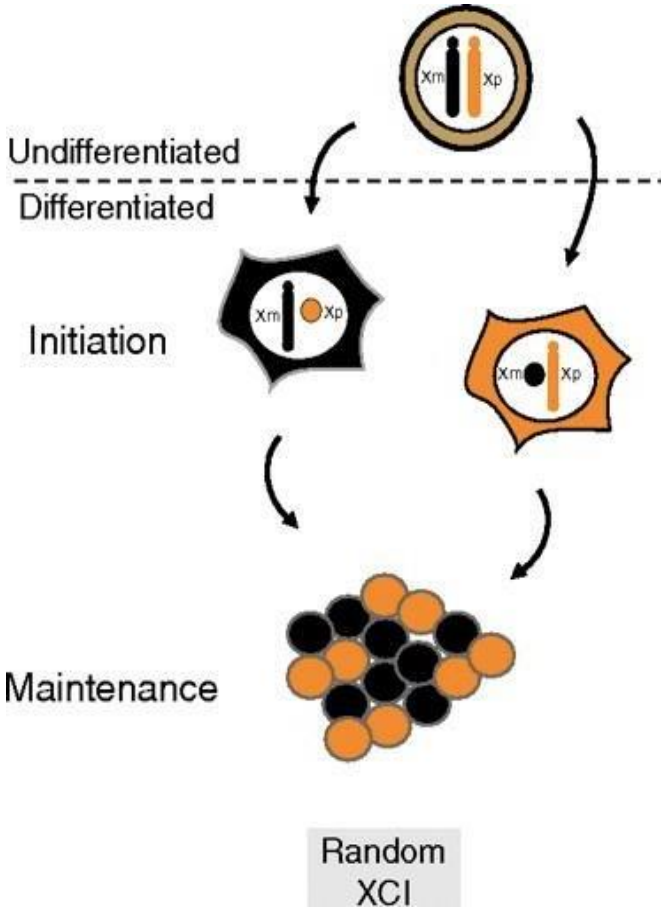


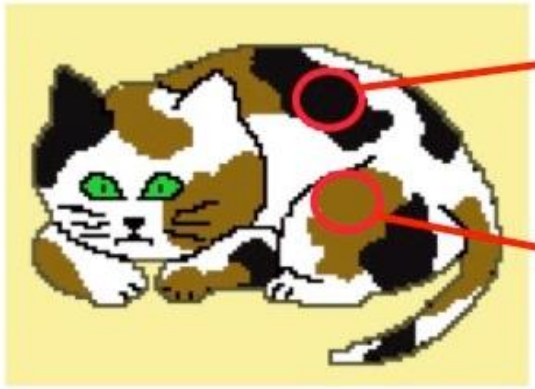
1 in 600 boys, Infertile, subtle symptoms

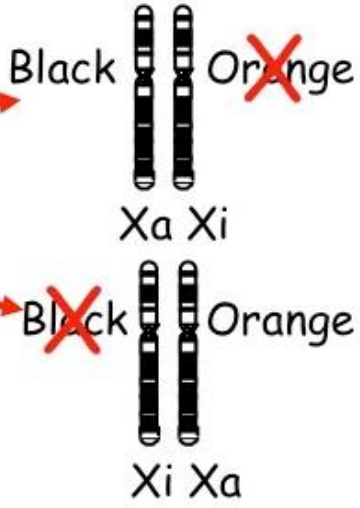
Why X aneuploidy is tolerated?

- X aneuploidy in humans is relatively common
- X chromosome upregulation:
  - Turner syndrome (X0);1/2,500 girls
- X chromosome inactivation:
  - Klinefelter syndrome (XXY); 1/600 boys
    - XXXY
    - XXX
- Mild effects caused by XCI-escape genes

Example of XCI







Random, Stable, Early

Summary on XCI

- Number of inactive X
- Mechanism of XCI
- Escaping XCI
- Genetic diseases associated with abnormal sex chromosomes

Questions

How many X chromosome does a Klinefelter syndrome (XXXY) body inactive?

https://www.polleverywhere.com/multiple_choice_polls/yIZ19gXrKpvfE64

A. 0

B. 1

C. 2

D. 3

Questions

Which of following statement is incorrect

https://www.polleverywhere.com/multiple_choice_polls/rgnXcwLMBn5DIco

A. Both genomic imprinting and XCI are regulated by epigenetic mechanisms also seen in cell differentiation.

B. Epigenetic markers except imprints are erased during embryonic development.

C. Parental conflict hypothesis refers to parents has a lot of disagreements and fights.

D. Large offspring syndrome and Beckwith-Wiedemann syndrome could both caused by sub-optimal culture conditions.