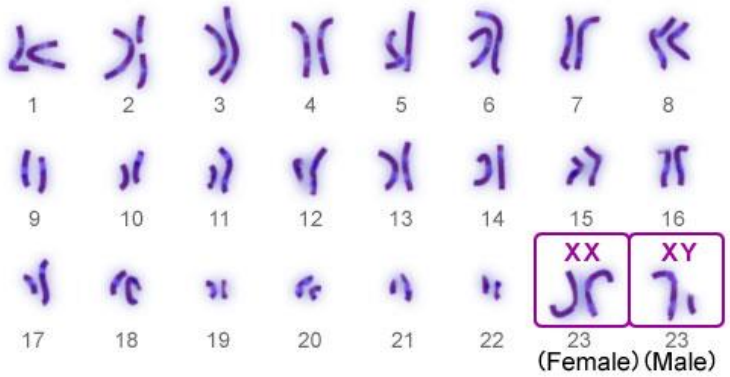
X Chromosome Inactivation

Recap: sex chromosomes

Somatic human cells have 46 chromosomes: 22 pairs of **autosomes** and two **sex chromosomes** (Figure 1). The pairs of autosomes contain copies of the same genes that may be identical or very similar. In **females**, the **two X** sex chromosomes are homologous, while **in males** the **X and Y** sex chromosomes are non-homologous. The X chromosome is rather large and gene-rich, while the Y chromosome is small and gene-poor.



NB! Chromosomes only look like this during cell division. Normally they are decondensed and entangled with each other.

Figure 1. Painted human chromosomes, arranged into pairs. Adapted from the National Taiwan Science Education Center.

One of the consequences of this are **sex-linked recessive genetic disorders**, such as colour blindness or haemophilia, which are much more common in males than in females.

Additional resources:

ThoughtCo. on sex-linked disorders

https://www.thoughtco.com/sex-linked-traits-373451

Haemophilia

https://www.hog.org/handbook/section/2/how-hemophilia-is-inherited

Gene dosage

Proteins are made, using the information copied from genes onto mRNA as a template. The amount of each protein is regulated on several levels, e.g. by how many mRNA templates are synthesised, how fast they are degraded, how likely the ribosomes are to bind them, etc. Naturally, the number of mRNAs is affected by the **number of copies of the gene** there are in the genome. An excessive number of any of the autosomes except chromosome 21 is lethal due to the large-scale protein imbalance. Trisomy of the gene-poor chromosome 21 is

the only one compatible with life, but it leads to a physical and mental retardation called Down syndrome.

Additional resources:

Nature Education on chromosomal abnormalities

https://www.nature.com/scitable/topicpage/chromosomal-abnormalities-aneuploidies-290

Wikipedia on Down syndrome

https://en.wikipedia.org/wiki/Down_syndrome

Wait a minute. How come then women can have two copies of the gene-rich X chromosome, of which men only have one, and be perfectly fine?

X chromosome inactivation

The answer to the above question lies in the event that happens during the early development of a female organism in each of its cells. One of the **X chromosomes** is randomly selected and **inactivated**. It forms a compact, transcriptionally inert structure called the **Barr body** (Figure 2). This inactivation is irreversible, and hence all the descendants of a given cell will have the same inactive X chromosome.

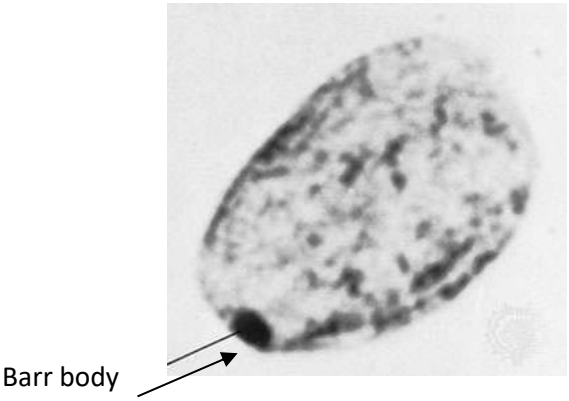


Figure 2. The nucleus of a human female cell with the Barr body clearly visible. From Encyclopaedia Britannica.

Task

In Figure 3, you see a female tortoiseshell cat. Can you think of how its fur colour develops?

Will a cloned cat be identical to the parent?

Figure 3. Female tortoiseshell cat. Image from Imartin6 via Wikimedia Commons.

The epigenetic mechanisms

The choice of which chromosome to inactivate is one of the crucial points during female development. Cells must first of all correctly "**count**" their X chromosomes: inactivating both chromosomes or failing to inactivate either will have deleterious consequences. Thanks to this robust counting mechanism, males with more than one X chromosome (XXY, XXXY etc. - Klinefelter syndrome) as well as females with one or three X chromosomes (X – Turner syndrome; XXX – Triple X syndrome) are viable, although often infertile. Thus, there should always be exactly one active X chromosome; once a normal cell starts inactivating one of the chromosomes, it should stop trying to inactivate the other. However, the exact mechanism of X chromosome counting is still poorly understood and is an active area of research.

Task

Why are people with an odd number of chromosomes (e.g. women with Triple X syndrome) usually infertile?

In addition, once a decision to inactivate one of the chromosomes is made, it must be **silenced completely**. This is achieved through action of two non-coding RNAs, **Xist** and **Tsix**. Those originate from the same genetic locus, but are "antisense", i.e. transcribed in opposite directions (Figure 4). Furthermore, each of them represses transcription of the other (the mechanism of which is currently unclear), resulting in a "**tug of war**" between the two. If Xist wins the battle and suppresses Tsix completely, such that it does not "stand in the way", it is produced in large quantities, spreads and coats the whole chromosome (Figure 5). If Tsix wins, it suppresses Xist transcription and spreading.

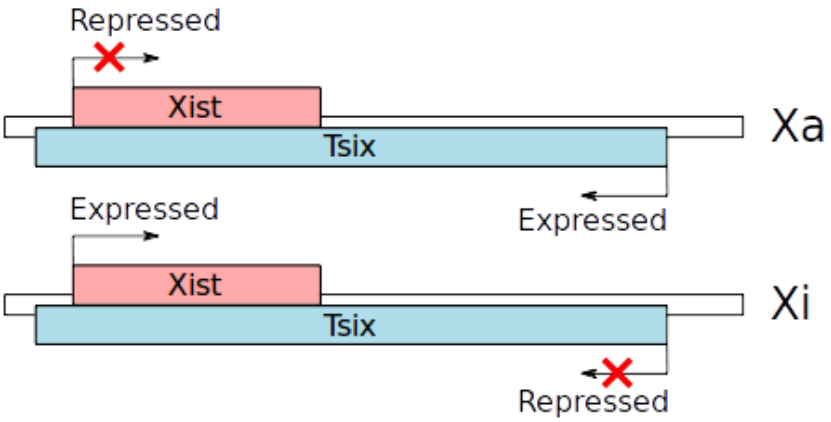


Figure 4. Xist and Tsix are antisense non-coding RNAs. Xist is transcribed on the inactive X chromosome (Xi), Tsix – on the active one (Xa).

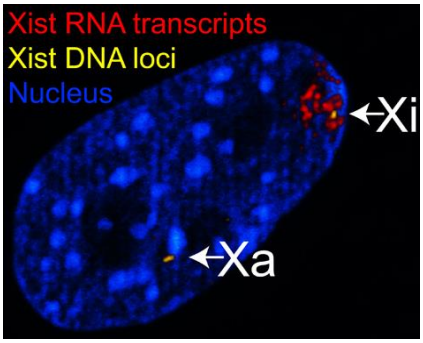


Figure 5. A microscope picture of a female cell nucleus, with the DNA painted blue. Xist RNA coats the whole inactive X chromosome (Xi), but is completely absent from the active X chromosome (Xa). Adapted from Reinius et al, BMC Genomics 2010.

Xist establishes the **silent chromatin state** on the inactive X chromosome, which is characterised by a high degree of DNA methylation, low level of active and high level of inactive histone marks, as well as special histone variants and a high degree of compaction.

This example clearly illustrates the complexity, but also the fine balance between the regulatory forces that allow the correct functioning of each cell. Epigenetic mechanisms do not act in isolation, but instead form a sensitive system that enables development, adaptation and other complex characteristics of life.

Task

Although in placental mammals (including us) X inactivation is random, in earlier marsupials (e.g. kangaroos) the paternal X chromosome is silenced in all cells of the body. What could be the evolutionary advantage of random inactivation?

Additional resources:

Nature Education on X chromosome inactivation

https://www.nature.com/scitable/topicpage/x-chromosome-x-inactivation-323