X chromosome inactivation

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Figure 1. Tortoiseshell cat A nice example of X inactivation can be observed in the fur of tortoiseshell and calico cats. The gene for fur coloration resides on the X chromosome, while each of the two X chromosomes codes for a different colour: black or orange. In an orange 'patch', only the X chromosome encoding the orange colour is active, while in the black 'patches', only the X chromosome encoding the black colour is active.

Each cell in a woman's body contains two X chromosomes. One of these chromosomes is switched off, because nobody can live with two active X chromosomes. Hendrik Marks and Henk Stunnenberg, molecular biologists at Radboud University Nijmegen, have shown the mechanism of spreading of this inactivation over the X chromosome, together with the group of Joost Gribnau from Erasmus MC in Rotterdam. The scientific journal *Genome Biology* will publish the results; a provisional PDF can already be found online.

In terms of sex chromosomes, men have a single X chromosome as well as an Y chromosome, whereas women have two copies of the X

chromosome. A process called X inactivation makes sure that one of these X chromosomes becomes inactivated in females during early embryonic development. A random process determines which of the two is switched off (Figure 1).

Xist 'jumps'

During normal embryo development, X inactivation in females takes place at a very early stage. Others had already discovered that the molecule 'Xist' is key during X inactivation. In order to further study this process, Marks and his colleagues used embryonic stem cells as a model system to study X inactivation. With the latest technology, they were able to keep the two X chromosomes apart and measure one of them – with its 166 million base pairs – in detail. Every day they checked which parts of the chromosome had been switched off. "The whole process took about eight days," Marks explains "and the inactivation spreads out from the centre of the X chromosome towards the ends. That doesn't happen gradually but moves jumpwise from domain to domain" (Figure 2).

Domains

"Domains are long pieces of DNA that cluster together in knots. As X inactivation jumps from domain to domain, we now know that these domains are co-regulated. It is very likely that diseases that are linked to incorrect inactivation of the X chromosome are due to improper spreading across domains."

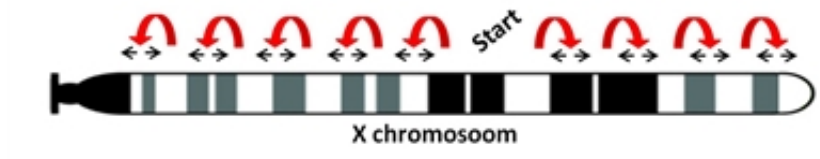

Figure 2. X chromosome inactivation “jumps” from one domain to the other.

Future plans

After one of the X chromosomes has been inactivated, it will stay inactive forever. In the future, Marks hopes to discover why sometimes the one while in other cases the other X chromosome is inactivated during development. That could help in treating X-linked diseases – like Rett syndrome and fragile X syndrome. "Reactivating (part of) the 'right' X chromosome could be a potential treatment for these diseases. So the next step is to figure out how to do that."

More information: "Dynamics of gene silencing during X inactivation using allele-specific RNA-seq." *Genome Biology* 2015, 16:149 DOI: 10.1186/s13059-015-0698-x

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