New insights into infertility-causing sex chromosome disorders

January 27 2017

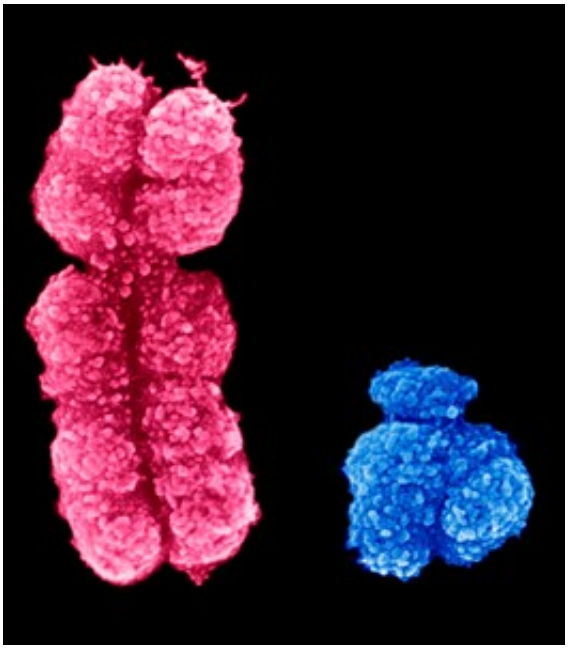

Image: X and Y chromosomes. Males have an X sex chromosome (pink) and a Y sex chromosome (blue) and females have two X sex chromosomes. Credit: Science Photo Library

Research carried out by Francis Crick Institute scientists provides new insights into sex chromosome disorders which typically cause infertility, such as Turner syndrome and Klinefelter syndrome. Through their research, the scientists have discovered an exception to a 'rule' or 'principle' of chromosome biology first hypothesised in 1967.

Our sex - male or female - is determined by the pair of sex chromosomes we have in our cells. Females have two copies of the gene-rich X chromosome but males have only one X chromosome, plus a much smaller sex-determining Y chromosome.

This difference creates a biological problem, as females have double the dose of the genes on the X chromosome. To account for this there is a process of 'dosage compensation' which balances the dosage, so that females have the same dosage from the X chromosome as males, not double.

The hypothesis of 'dosage compensation' was proposed by Susumu Ohno in 1967 and experiments have confirmed that this process does indeed take place within cells, by mechanisms which vary from organism to organism. His hypothesis took on the status of a rule; it was assumed that dosage compensation would be found within all cells.

Using RNA sequencing, James Turner's group discovered that mouse and human germ cells, which develop into gametes, i.e. sperm and eggs, do not conform to Ohno's 'rule' of dosage compensation.

Germ cells are special because they have to be able to give rise to the creation of a brand-new organism, with all its different types of tissue and organs and structural complexity. In order to be able to do this germ cells undergo a process of genome-wide 'reprogramming', in which information from the previous generation is erased.

The scientists suspected that this 'reprogramming' could disrupt dosage compensation within those germ cells. Their experiments demonstrated that their hypothesis was correct: in male germ cells expression from the X chromosome was very low, while in female germ cells it was very high.

The discovery of this exception to Ohno's rule of dosage compensation provides new insights into a key topic of developmental biology, namely the development of an organism's sex.

James Turner said: "The discovery challenges the idea that germ cells are initially 'sex neutral' before the Y chromosome 'kicks in' and instructs the gonad to develop into either a testis or an ovary. Our research demonstrates that prior to any overt 'fork' in development the germ cells are already sex-differentiated; they have different and imbalanced X chromosome dosages."

The research is clinically significant because it provides a better understanding of the biology underlying sex chromosome disorders, such as Turner syndrome, which affects about 1 in every 2,000 females and Klinefelter syndrome, which affects around 1 in every 660 males. Both of these syndromes typically cause infertility.

The Crick scientists looked at germ cells within Turner and Klinefelter syndrome mice. To their surprise, they discovered that germ cells in female Turner syndrome mice display the dosage found in normal male germ cells. They also discovered that germ cells in male Klinefelter syndrome mice display the dosage found in normal female germ cells. Their hypothesis is that the cause of infertility is this confusion, or conflict, between the sex of the organism, in terms of the presence or absence of the Y chromosome, and the sex identity of the germ cell, in terms of its X chromosome dosage.

More information: Mahesh N. Sangrithi et al. Non-Canonical and Sexually Dimorphic X Dosage Compensation States in the Mouse and Human Germline, *Developmental Cell* (2017). DOI: 10.1016/j.devcel.2016.12.023

Provided by The Francis Crick Institute