Mary Lyon's brilliant and illuminating conjecture

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A general finding in animals is that the correct dosage of genes is two, with one copy inherited from each parent. Deviation from this *diploid* condition typically leads either to abnormality or lethality. That in mammals the X-chromosome carries many genes that are absent from the much smaller male-determining Y-chromosome clearly seems to pose a dosage problem. One suggestion for addressing this was that genes on each X in females might be expressed at half the level of those on the single X in males. However, there was no obvious precedent for such a possibility.

In 1961 Mary Lyon offered a most elegant solution to the problem in a paper in the journal *Nature* which was not only a model of clarity and brevity but has withstood the test of time. She addressed the issue by making three deductions from just two observations in mice. Among other things, her conjecture offers a compelling explanation as to why females are much less susceptible to adverse effects of mutation of genes carried on the X-chromosome than males.

Mary Frances Lyon was born in Norwich in 1925 as the eldest of three children but the family moved several times during her childhood for her father's work. Mary's secondary education began at King Edward VI High school for Girls in Birmingham where she developed a passion for Biology and it continued at Woking High School from where she had to cycle some distance to at least two other schools to obtain the necessary advanced instruction in the sciences and mathematics. When the time came for her to sit the Entrance Exam for Cambridge University she realised that this included compulsory Latin which she had never studied.

However, she managed to learn enough of the subject in 6 weeks to pass the Exams and be admitted to Girton College. As a woman she did not qualify for a full degree but was awarded just a 'titular' one, a miscarriage of justice that was finally rectified by the University at a Special Ceremony in 1998.

Mary started research in genetics at Cambridge under the supervision of the eccentric Sir Ronald Fisher of statistical fame but could not relate to him and thus moved to Edinburgh to complete her PhD under Douglas Falconer (Figure 1). In 1954 she moved with Toby Carter's Group to MRC Harwell where she spent the entire remainder of her research career. In 1962 she was made head of the Genetics Section at Harwell. From 1971 she lived in Crabtree Cottage near Abingdon until her death on Christmas Day 2014. For the last decade of her life she suffered from Parkinson's Disease but this did not prevent her from maintaining an active interest in mouse genetics.

So what made Mary's contribution to mammalian genetics so special? To understand this, we need to note that the normal action of a gene depends on its being present in two copies or doses, one from each parent. Absence of one copy or presence of more than 2 is associated with abnormal development or function. An example of this is Down Syndrome which is due to the presence of extra genes due to inheritance of three rather than the normal 2 copies human chromosome 21. However, when we look at the sex chromosomes, X and Y, we are confronted with a problem of dosage because the X- carries many more genes than the Y-, a difference estimated to be of the order of tenfold in the human. In the 1950s, several researchers grappled unsuccessfully with the problem of how the effective dosage for such genes could be equalised between female with 2 X-chromosomes and males with just one. It was Mary Lyon in 1961 that came up with the correct solution to this problem with what Sir Henry Harris, a previous Regius Professor of Medicine at Oxford, described in a book "as one of the most brilliant and illuminating conjectures in the history of embryology".

Figure 1. Mary Lyon in the Genetics Department of the Institute of Animal Genetics in Edinburgh in 1950. © Medical Research Council.

So what was this solution? In a very brief paper published in Nature[1] in 1961 Mary drew 3 conclusions from 2 observations.

1. Mice with just one X chromosome and no Y i.e. XO mice were essentially normal fertile females, so that only a single X was necessary for normal development and function. This is not quite true in humans where XO individuals are infertile, as Turner's Syndrome cases.

2. Females that inherit X chromosomes carrying different forms (alleles) of genes affecting coat colour or texture do not show typical uniform Mendelian dominance of one form over the other or a uniform intermediate state, but multiple patches of each type.

From these observations Mary drew the following three conclusions regarding the behaviour of the two X-chromosomes in female embryos.

1. Very early in embryonic development one X chromosome is switched off (inactivated) in every cell.

2. It is random whether the maternally or paternally inherited X is switched off in any given cell.

3. Inactivation is a stable heritable property in that once a cell has switched off the maternal or paternal X all its (clonal) descendants have the same X inactive.

One significant consequence of X-inactivation is that female mammals are genetically mosaic for all genes in which parents contribute distinct variants (alleles). As a consequence, women who receive an X-link haemophilia mutation from one parent and the normal variant from the other, typically have enough cells expressing the normal variant or allele to protect them from adverse effects of the mutant one. Of course, no such protection is afforded to males who happen to receive the mutant X from their mothers.

As is often the case, truly novel ideas often seem with hindsight to be rather obvious. Thomas Henry Huxley, nicknamed 'Darwin's Bulldog' for his robust defence of Darwin, is reputed to have responded to being made aware of the concept of natural selection with "why didn't I think of that?".

Many share my view that Mary should have received the Nobel Prize for her discovery and it is very hard to understand why she did not. However, in honour of her achievements, the MRC established the Mary Lyon Centre at Harwell in 2004.

Of course, no human being is perfect and Mary Lyon had two conspicuous vices. The first was a serious addiction to all forms of chocolate and the second a marked propensity to cheat at party games like musical chairs!

Mary suffered from Parkinson's disease for more than a decade following her formal retirement but this in no way impaired her intellectual commitment to mouse genetics or her encyclopaedic memory regarding mouse mutations.

In conclusion, Mary was one of the really great pioneers of 20th Century biology and serves as an excellent role model for Women in Science.

Reference

1 **Lyon, M.F.** (1961). Gene action on the X-chromosome of the mouse (*Mus musculus L*). Nature 190, 372-373.