Mary F. Lyon

(1925–2014)

Grande dame of mouse genetics.

In 1961, Mary Frances Lyon proposed in *Nature* that one of the two X chromosomes in every cell of female mammals is inactivated. This, she argued, occurs to prevent XX female cells from expressing twice as many X-linked gene products as XY male cells.

Lyon's X-chromosome inactivation hypothesis had profound implications for clinical genetics and developmental biology. For instance, it helped researchers to elucidate the genetic basis of many X-linked diseases, such as Duchenne muscular dystrophy. It also led, 30 years later, to the discovery of the *Xist* gene, which helped to spawn a whole field of research on the role of long non-coding RNA molecules in regulating gene expression. The non-coding Xist RNA is the master switch that turns off the X chromosome. It also explains some everyday phenomena, such as the patchy colouring of tortoiseshell cats.

Lyon died aged 89, on Christmas Day 2014, after drinking a glass of sherry, eating her Christmas lunch and settling down in her favourite chair for a nap. She was born in Norwich, UK, in 1925, the eldest of three children of a teacher mother and civil-servant father. An inspirational teacher at her grammar school sparked her interest in biology and in 1943 — when women were awarded only 'titular' degrees — she went to Girton College, University of Cambridge, to study zoology.

In 1946, Lyon started her PhD at Cambridge with the geneticist R. A. Fisher in the emerging field of mouse genetics. In 1948, in pursuit of better histology facilities to complete her doctoral studies, Lyon moved to the Institute of Animal Genetics at the University of Edinburgh, at the time headed by the embryologist C. H. Waddington, another figure whose work profoundly influenced her.

Lyon stayed in Edinburgh to work on a project funded by the Medical Research Council (MRC) to study mutagenesis in mice under the geneticist Toby Carter: in the 1940s there was widespread concern about the possibility of atomic-weapons testing causing mutations. In 1955, Carter transferred his group to the MRC Radiobiology Unit at Harwell, UK, where there was more space for mouse breeding. It was during this period that Lyon observed the patchy coats of female mice carrying X-linked coat-colour mutations. This, coupled with the knowledge that female mice carrying a single X chromosome are viable, led her to propose the hypothesis of X-chromosome inactivation.

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Apart from a short sabbatical in Cambridge, Lyon remained at Harwell for the rest of her career. From 1962 she was head of the genetics division, which became an independent Mammalian Genetics Unit in 1995.

Despite some initial tussles with the MRC over the amount of time and resources to devote to 'ancillary projects' in developmental genetics — rather than to establishing the hazards of radiation and other mutagenic agents — Lyon managed to pursue both.

Throughout her six decades of work on mice, her favourite chromosome, aside from the X, was 17. Chromosome 17 encodes the t-complex, a genetic anomaly found in certain wild mice that gives rise to different 't-haplotypes', which consist of different DNA rearrangements. Certain t-haplotypes are preferentially transmitted by males to their offspring; mice carrying two copies of the same t-haplotype are either not viable or sterile. By carrying out a series of clever genetic crosses, Lyon worked out what was going on. This work made a major contribution to the understanding of phenomena such as non-Mendelian inheritance (the abnormal segregation of chromosome pairs from the expected one-to-one ratio) and the effect that inversions — when a segment of a chromosome is reversed — have on suppressing chromosomal recombination.

Lyon was a central figure in twentieth-century mouse genetics. She laid the intellectual foundations and developed the genetic tools for the use of mice as model organisms in molecular medicine, cell and developmental biology and in deciphering the function of the human genome. Lyon was editor of *Mouse News Letter* from 1956 to 1970, a publication that had a key role in establishing a mouse-focused research community in the pre-Internet age. She also helped to develop a common language for the field by chairing the Committee on Standardised Genetic Nomenclature for Mice from 1975 to 1990. Her pivotal contribution was recognized by the naming of the Mary Lyon Centre, an international facility for mouse-genetic resources, opened at Harwell in 2004, and by the creation of the Mary Lyon Medal by the UK Genetics Society in 2014.

Because everything Mary said was so carefully thought through, she could be difficult to talk to: on the phone, it was easy to think you had been cut off. She did not suffer fools gladly, but was a great supporter of the bright young scientist, often eschewing authorship of publications to enhance the profile of junior collaborators. She was intellectually rigorous but not dictatorial. When I began my PhD with her in 1977, she gave me a handful of papers, showed me the genetic tools — mice carrying the various mutations and chromosomal rearrangements — and said, "do something on X-inactivation". That degree of academic freedom was exhilarating, coupled as it was with the safety net of robust critique.

Among numerous other honours, Mary was a foreign associate of the US National Academy of Sciences and was the 28th eighth woman to be elected a fellow of the Royal Society in London in 1973. She might have been elected sooner had leading geneticist Hans Grüneberg not initially disbelieved the Lyon hypothesis. It is perhaps surprising that Mary did not receive any establishment honours, but bureaucracy, politics and networking were alien to her.

Her first love was mice, although she always had a cat — a tortoiseshell, of course. ■

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