EMBARGOED UNTIL 18.00 UK TIME/13.00 US EASTERN TIME

What Sex did to the X – and Why

A chromosome account of evolution and revolution

The human X chromosome is about sex and how it evolved. It also has a unique position in the history of genetics – and the genetics of history.

On Thursday 17 March 2005, an international team led by the Wellcome Trust Sanger Institute, Cambridge, UK publishes in *Nature* the most complete analysis of this remarkable chromosome. Other major contributions to the sequence came from groups at Baylor College of Medicine, Houston TX, USA, Institute for Molecular Biotechnology, Jena, Germany, Washington University Genome Sequencing Center, St Louis, MO, USA and Max-Planck-Institute for Molecular Genetics, Berlin, Germany.

The landmark study shows how we got an X chromosome and how it has been preserved (while the Y chromosome has degenerated). It also identifies new genes involved in disease and provides a gold-standard platform for studies to understand, to diagnose and, it is hoped, to treat a huge range of human disease.

The human X chromosome has a different biology to all others. Whereas females have two X chromosomes, males have only one X chromosome and a Y chromosome, which is an eroded version of the X chromosome, containing only a few genes.

The consequences are dramatic; any defects in genes on the X chromosome are often apparent in males because the Y chromosome does not carry corresponding genes to compensate. For mutations on the X chromosome, the diseases are, most often, diseases of males – and not of humankind.

More than 300 diseases have been mapped to the X chromosome – by far the highest proportion of any chromosome – including Duchenne Muscular Dystrophy (DMD) and haemophilia. The genome sequence has been used in the isolation of more than 40 genes that are involved in medical conditions, including cleft palate and blindness.

‘From studying such genes, we can get remarkable insight into disease processes,’ says Mark Ross, Project Leader at the Wellcome Trust Sanger Institute. ‘From our study of one gene involved in an X-linked disease, a genetic test was developed and a new pathway that controls the workings of the immune system was discovered.

‘But the importance of the sequence goes beyond the biology of individual genes. We have also gained a deep insight into the evolution and biology of the whole chromosome. We can see the way evolution has shaped the chromosomes that determine our gender to give them their unique properties.’

These remarkable chromosomes evolved from humble beginnings as an ‘ordinary’ pair of identical chromosomes. It is thought that changes to a gene on one of the pair created the key switch in the pathway to male development and set in train the degeneration of this chromosome. As this emerging Y chromosome eroded, maintaining the integrity of the X chromosome was essential. When the integrity is compromised in human males, disease often results.

‘The X chromosome was pivotal in early human genetics because we were able to see clearly how mutations cause disease,’ said Dr Bentley, Head of Human Genetics at the Institute. ‘There are many more genetic disorders on the X chromosome where the underlying gene is still to be found. Now we can make use of the finished sequence to find them. These discoveries will have a major impact on our understanding of many fundamental biological processes.’

The X chromosome played an important part in developing the methods of genetics in the molecular age. One of the first genes cloned using modern methods was that involved in Duchenne Muscular Dystrophy. For genes such as DMD, diagnosis has been transformed by genomic sequence and we are beginning to see hopes for new treatments based on that understanding.

There remain many conditions that are associated with genes on the X chromosome for which a genetic basis is lacking. In simple cases, a 'candidate' gene can be identified and tracked down. For more complex diseases, more than one gene may be involved and the hunt is much more difficult and the path littered with false clues and false dawns. However, new methods that make use of the sequence are being developed to identify genes involved in common disease.

'The detailed analysis of the sequence of the human X chromosome is a monumental achievement. This work represents yet another exciting example of what we can learn from the vast trove of sequence data produced by the Human Genome Project and made freely available to researchers around the world,' says Francis S. Collins, MD, PhD, director of the National Human Genome Research Institute, which along with the U.S. Department of Energy, led the Human Genome Project in the United States.

The X chromosome has played its part in political history: X-linked human diseases include haemophilia, in which the blood fails to clot properly. Queen Victoria was a 'carrier' of haemophilia and passed it to her own children and, through them, to the Royal families of Europe. It has been argued that inheritance of haemophilia by Alexei, son of the last Tsar of Russia, led indirectly to the Russian Revolution.

This chromosome has also been vital to biomedical history: from the first gene mapped in the human – red-green colour blindness in 1911 – to searching for an understanding of human diseases, this unique chromosome has taught us an enormous amount about genetics and human biology. From the sequence, much knowledge has already been wrested, but there is much more of the X to understand.

###ENDS###

Notes to Editors

Publication:

Ross MT *et al.* (2005) The DNA sequence of the human X chromosome. *Nature* **17 March 2005**

Additional Materials

- X chromosome in numbers and pictures
- Backgrounder – X chromosome and disease
- Backgrounder – X chromosomes and sex
- Backgrounder – X in history

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The Wellcome Trust Sanger Institute, which receives the majority of its funding from the Wellcome Trust, was founded in 1993 as the focus for UK sequencing efforts. The Institute is responsible for the completion of the sequence of approximately one-third of the human genome as well as genomes of model organisms such as mouse and zebrafish, and more than 90 pathogen genomes. In October 2001, funding was awarded by the Wellcome Trust to support a new range of postgenomic programmes designed to understand the biological function of genes and their relevance to our health. These programmes are built around a Faculty of more than 30 senior researchers.
http://www.sanger.ac.uk

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