The X factor

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The sequence of the 'feminine' X chromosome is a prime hunting ground for geneticists interested in the evolution of the cognitive and cultural sophistication that defines the human species. Erika Check reports.

This January, Harvard University president Larry Summers incited a near riot by suggesting that men might be better than women at science. The resulting pandemonium has revealed few genuine insights into male and female mental abilities — although it has shown that old prejudices linger on campus, and beyond.

In contrast, biology presents a challenge to those who still believe women are better off at home than in the hallowed halls of universities. As geneticists search for the roots of humanity's unique mental abilities, they are beginning to pay close attention to the 'feminine' X chromosome. Women have two copies of this chromosome, whereas men have only one. And the complete sequence of the X chromosome, published in *Nature* this week[1] (see also News and Views, page 279), confirms that an unusually large number of its genes code for proteins important to brain function.

Why this should be the case is sparking debate among evolutionary biologists. And some are even suggesting that the X chromosome will tell us why we are different from our closest relatives — why we can write poetry and design nuclear weapons, but chimpanzees can't. In a sense, they argue, the feminine chromosome could hold the secrets of humanity. "We used to think that the X was boring," says Jenny Graves, an evolutionary geneticist at the Australian National University in Canberra. "Now we're seeing just how wrong we were."

Today's understanding of the X chromosome helps to explain a puzzling observation from the late nineteenth century, when doctors combing through data from the 1890 US Census noticed that more boys than girls were mentally disabled[2]. We now know that this reflects a preponderance of genes for brain function on the X chromosome. A woman uses only one of her two X chromosomes in each cell, so if one of her X chromosomes has a defective gene, only some of her cells will suffer. But men have only one X, so any defective brain genes from that chromosome are invariably expressed.

> "If higher cognitive abilities were a critical step in our evolution, it makes sense that you'd find those functions on the X chromosome."
> — Hunt Willard

All in the mind

Many different types of mental retardation have since been linked to defects in genes on the X chromosome — far more than can be explained by their chance distribution throughout the genome. According to one analysis, there are 221 known human genetic defects that can cause mental impairment, some 10% of which reside on the X chromosome, even though it carries less than 4% of known human genes[3].

Detailed studies have also shown that the specific genes linked to mental disabilities play crucial roles in normal brain function[4]. For instance, more than a decade ago, an international team reported the discovery of the gene that causes fragile X syndrome[5], a disorder that leads to a range of problems including mental disability. Scientists now know that the defective gene, called *FMR1*, normally makes a protein that is involved in shuttling the genetic messages that enable nerve cells to send signals through the brain[6]. Another gene, known as *MECP2*, leads to a whole range of mental disorders when mutated; its protein seems to be involved in the silencing of other genes required for normal learning, memory and the growth of brain cells[4].

It's still a giant step from understanding defects in single genes to proving that the X chromosome allows us to write novels and solve calculus equations. But there is some indirect evidence that genes on the X chromosomes are involved in higher cognitive functions. One hint comes from a study of 4,000 sets of British identical twins. Each female twin inherits two X chromosomes, one from her mother and one from her father, but each individual twin randomly inactivates one of her two X chromosomes. So identical twin sisters can express different X-chromosome genes. In contrast, male identical twins

inherit only one X chromosome, from their mothers, and so must activate the same X-linked genes. In the British study, researchers led by Ian Craig of King's College London found that in some traits linked to intelligence, such as verbal skills and good social behaviour, male twins were more alike than female twins[7].

But why should the X chromosome have emerged as a hotspot for genes influencing our cognitive abilities? Evolutionary geneticists believe that the two mammalian sex chromosomes, X and Y, were once identical. As mammals began to diverge from their reptilian ancestors, some 300 million years ago, the proto-X and proto-Y chromosomes took on the role of determining an individual's sex. Both initially started accumulating genes from elsewhere in the genome, but over time the two chromosomes began to grow apart; the Y started to shrink and lost many of its genes.

Solid foundation

Eventually, the sex chromosomes diverged to the point where they were no longer able to exchange genetic material during the cell divisions that give rise to sperm and eggs, as do the members of every other pair of chromosomes. This has left the X chromosome as one of the most stable in the mammalian genome — which paradoxically may have exposed its genes to more intense pressure to evolve.

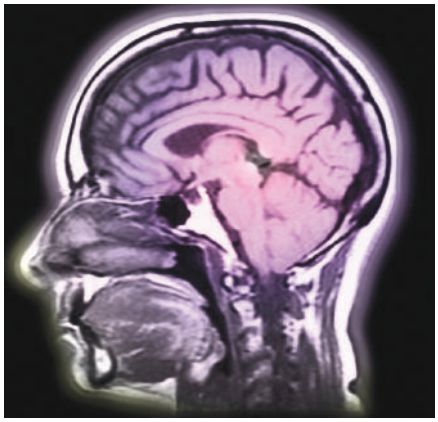
The X chromosome gets a chance to shine, or to fail miserably, each time it passes through the male line. Because a male carries only one copy, any new mutations are revealed in all their glory. And because successful males have the potential to sire very large numbers of children with multiple partners, mutations on the X chromosome that are advantageous to both sexes can spread rapidly through a population.

In our own species, where intelligence and social skills are thought to be central to success, genes on the X chromosome seem to have evolved rapidly to provide us with the necessary brain power. "If higher cognitive abilities were a critical step in our own evolution, it makes sense that you might find those functions on the X chromosome," says Hunt Willard, a human geneticist and director of the Institute for Genome Sciences and Policy at Duke University in Durham, North Carolina.

Provocatively, researchers led by Horst Hameister at the University of Ulm in Germany speculate that this process was driven by sexual selection[3]. Early in human evolution, they suggest, females developed a preference for intelligent males. According to their theory, the genes for super-intelligence and for the preference of intelligent males were closely linked, and so were inherited together. And because superior intelligence also aided survival, the process wasn't kept in check by natural selection — unlike other sexually selected characteristics such as the peacock's tail, which makes its bearers more vulnerable to predators.

Double vision: by looking for differences in the behaviour of twin girls, geneticists are trying to find out how X chromosomes (top) influence mental ability.

Many of the genes on the X chromosome associated with human brain function seem to have distant relatives with different functions in other vertebrates, such as chickens and fish[8]. So in boosting our cognitive abilities, the X chromosome seems to have co-opted a diverse range of existing genes, rather than evolving a new set of genetic sequences for the purpose. "These old genes are getting new use," says Hameister.



Head start: our large brains may have evolved thanks to the action of the X chromosome.

In some instances, geneticists have pinpointed genes on the X chromosome that still seem to be in the process of adopting new roles in the brain. For instance, a gene called *JARID1C* seems to be evolving from a similar gene called *JARID1D*, which is found on the Y chromosome. If men inherit a damaged version of the *JARID1C* gene on their single X chromosome, they develop mental disabilities. The fact that the healthy Y chromosome version cannot compensate for its defective cousin hints that *JARID1C* is becoming more crucial to the brain as it evolves[9].

Personality profiles

Geneticists are now gearing up to go after other X-linked genes that may help explain what makes us human. In London, Craig's team plans to identify twins who score high or low on certain 'people skills', such as sharing their toys and volunteering help to others. The researchers will then use gene chips to scan the twins' DNA, looking for particular genetic variations that correlate with these traits. Once they find a region of DNA that seems to link to a particular trait, the group will look at the detailed sequence of individual chromosomes to try to pin down the exact gene involved. The X chromosome data, with its wealth of information about human brain genes, is likely to feature prominently in this endeavour.

Other researchers plan to continue the quest for genes involved in X-linked brain disorders. Every two years, for instance, scientists meet as part of a European consortium that catalogues genes involved in such conditions. Researchers believe that the information so far gleaned about human brain function from these studies barely scratches the surface.

If we want to understand the cognitive 'X factor' that separates us from the rest of the animal kingdom, then it seems that the X chromosome is the place to start looking. In the meantime, Summers and his acolytes can chew on this thought: even if there's any truth in the idea that men are more suited to a career in science than women, they just might owe this mental predisposition to the 'girly' chromosome. ■

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