Biology

Master gene makes maleness mandatory

In the Broadway production of "My Fair Lady," an exasperated Rex Harrison became famous for lamenting: "Why can't a woman – be more like a man?" Now, it seems, British molecular biologists have found the answer.

What women lack, these researchers say, is a single gene called SRY – or the Sex-determining Region of the Y chromosome. The finding culminates two decades of work in which scientists have sought to identify the specific Y-chromosomal region responsible for masculinity – not only to understand the genetics of gender but also as a model for studying basic principles of embryo development.

The gene's discoverers say that this newly identified string of nucleic acids, present within every male mammalian cell so far examined, embodies the very essence of maleness. In humans, for example, the gene seems responsible for initiating the creation of testes after about seven weeks of fetal development. The testes, in turn, produce a cocktail of masculinizing hormones that influence gender-related developmental pathways throughout a man's life.

Researchers have known since 1959 that male mammalian cells, except sperm, have both an X chromosome and a Y chromosome, while female mammalian cells, except eggs, contain two Xs. They've also known that only a small portion of the Y chromosome confers masculinity. Indeed, mutant XY mammals whose Y chromosomes lack this male-determining portion develop as females. And XX individuals who, through a genetic quirk, have this critical bit of Y appended to their X chromosomes, develop as males.

Previously reported discoveries of candidate genes for maleness – including the widely publicized, 1987 isolation of a testis-determining factor gene (SN: 1/2/88, p.4) – have all proven wrong. In the July 19 NATURE, Andrew H. Sinclair of the Imperial Cancer Research Fund in London and his colleagues say their newly discovered SRY is the best candidate yet. Others agree, but all concur that final confirmation depends upon an upcoming series of experiments in which scientists will try to create male mice by inserting the SRY gene into female mouse embryos. Sinclair says he and his co-workers hope to complete those tests by the end of the year.

Meanwhile, the evidence that SRY is indeed the master gene for maleness appears compelling. For example, a true male-determining gene would probably be highly conserved through evolution, and so could be expected in a wide variety of animals within a given class, such as mammals. Using a molecular test dubbed a "Noah's Ark blot," the London researchers found the gene in blood cells of human XX males, and in male chimpanzees, rabbits, pigs, horses, cattle and tigers. The gene was absent in all females tested.

Furthermore, in the same issue of NATURE, a team of researchers led by John Gubbay of the MRC National Institute for Medical Research in London describe experiments showing that XY female mice lack the mouse version of SRY. And they found that in embryonic male mice, the gene becomes active at about the time testes development begins. Those findings bolster the evidence for its role in male development.

Unexpectedly, mouse and human studies indicate SRY remains active in adult male testes, suggesting the gene has some ongoing function even after completion of male development. The nature of that function remains a mystery.

Scientists remain uncertain about how SRY may regulate other genes that play a role in gender development. Perhaps significantly, Sinclair says, SRY's nucleic-acid sequence resembles those of known DNA-binding proteins. Such proteins have the ability to turn other genes on or off. He speculates that the SRY protein might suppress genes required for female development, or activate genes whose products add up to maleness.

Biomedicine

Gene found for neurofibromatosis

When is a single gene not just a single gene? That's the riddle two research teams recently solved after a three-year hunt for the cause of neurofibromatosis, the disfiguring illness once identified as Elephant Man's disease.

In separate reports on July 13, Howard Hughes Medical Institute investigators announced that after several false starts, they had isolated the gene responsible for the illness, which afflicts some 100,000 Americans and causes uncontrolled proliferation of nerve cells that can result in lumpy growths under the skin or large tumors. The teams found that the gene contains three other genes within it, none of which appear to play a role in the illness, but which confounded efforts to find the actual culprit. Raymond L. White and his co-workers at the University of Utah School of Medicine in Salt Lake City reported their findings in CELL, and Francis S. Collins and his collaborators at the University of Michigan Medical Center in Ann Arbor detailed their study in SCIENCE.

Scientists in 1987 had found that the mutation responsible for neurofibromatosis lies within a region on chromosome 17 containing several hundred genes. They then narrowed their search to a small portion of the chromosome that had undergone a rare mishap in two patients – a piece of it had broken off and traded places with a fragment from another chromosome. The two teams isolated a total of three likely genes near the break point, but none were mutated in neurofibromatosis patients, which would indicate a link with the disease. However, a newly isolated larger gene near the fragmented region that contains the three others undergoes the telltale mutation, the researchers now report.

The researchers say the isolated gene will enable physicians to diagnose the illness early and quickly treat life-threatening tumors. In addition, if scientists can identify how the protein normally produced by the gene can control cell growth, it may lead to the first drug treatment for the disorder.

Smoking boosts death risk for diabetics

A new report suggests the well-known hazards of smoking are magnified for women who have Type I diabetes, the insulin-dependent form of this sugar processing disease.

Claudia Scala Moy and colleagues at the University of Pittsburgh studied 548 Type I men and women age 17 to 40. The team reports in the July CIRCULATION that smoking, especially heavy smoking, boosted the risk of death for both sexes, but especially for the female diabetics.

"Diabetics just shouldn't even think of smoking," diabetes specialist W. James Howard at the Medlantic Research Foundation in Washington, D.C. told SCIENCE NEWS. Howard wrote an editorial accompanying Moy's article.

Type I diabetic women have a risk of death 10 times higher than women of similar age in the general population, Moy reports. However, heavy smoking (a pack of cigarettes per day for five years) ups the chance of dying 20-fold for these diabetic women, the researchers found.

The Type I diabetic male's risk of death is generally six times higher than men in the general population, a figure that rises to 10 times greater for these men who smoke heavily.

The researchers can't explain the difference between the sexes, but speculate that smoking may give diabetic women a double-whammy risk of heart disease compared to their female peers in the general population. Diabetes predisposes people to heart disease and smoking may accelerate that process.

In a separate analysis, Moy's team found virtually identical smoking rates among 156 Type I diabetic and non-diabetic siblings. That suggests people with diabetes don't get or heed the anti-smoking message, despite their high-risk status and frequent contact with the health system, Moy says.