Gene variations sway prostate cancer risk

When it comes to prostate cancer, all men may not be created equal. Likely to be diagnosed in more than 300,000 men in the United States this year, prostate cancer remains relatively rare in Asia, Africa, and South America. Furthermore, black U.S. men have the world's highest incidence of the cancer, nearly 40 percent higher than even that of white U.S. men.

Cancer investigators have long struggled to explain these disparities, citing differences in diet, particularly the amount of fat consumed, as one of many possible contributing factors.

More recently, however, scientists have begun to build a compelling case that genetic variation among populations may account for much, perhaps even most, of the difference in prostate cancer risk. A new study now offers evidence that differences in a gene that encodes an enzyme crucial to the growth of prostate cells make some groups more susceptible to prostate cancer than others.

Made primarily in the prostate, this enzyme, 5-alpha reductase type II, converts testosterone to dihydrotestosterone (DHT). Though both hormones, known as androgens, can induce prostate cells to divide, DHT is the more potent of the two. In fact, finasteride, a drug used to shrink enlarged prostates, blocks the creation of DHT by inhibiting 5-alpha reductase type II.

A few years ago, a group headed by Ronald K. Ross of the University of Southern California School of Medicine in Los Angeles proposed that elevated concentrations of testosterone in the blood—and therefore increased DHT concentrations in the prostate—might explain the higher prostate cancer risk in some populations.

Ross' group has now taken a close look at the gene encoding 5-alpha reductase type II. Other researchers had reported that inheriting a mutated form of the gene, which codes for a nonfunctioning enzyme, causes a rare disorder in which men appear female at birth but during puberty develop the muscles, hair growth, and other outward physical features of their sex.

Ross and his colleagues have found that the enzyme's gene comes in two functional versions, or alleles. The enzymes produced by these alleles differ by a single amino acid: A valine replaces a leucine at one site.

The researchers then examined whether the different prostate cancer risks of black and Asian American men might result from the alleles they possess. Almost 60 percent of blacks have two copies of the valine allele, while only 30 percent of Asian Americans do, Juergen K.V. Reichardt, a member of Ross' group, reported at last week's American Society of Human Genetics Meeting in San Francisco.

Furthermore, the investigators have preliminary evidence that the leucine-containing form of 5-alpha reductase type II is far less efficient at converting testosterone to DHT than the valine-containing enzyme made by the other allele.

One reason few Asian Americans get prostate cancer may be that their 5-alpha reductase type II genes tend to encode the enzyme that does a poor job of making DHT, suggests Reichardt. In contrast, black men generally have the enzyme most proficient at creating DHT, he adds.

Reichardt cautions that his group has to examine further the different DHT-making efficiency of the two forms of the enzyme. In addition, by surveying even more people, the researchers hope to confirm that racial or ethnic population differences exist in the distribution of the enzyme's alleles.

"It's an attractive hypothesis, but it certainly isn't ironclad yet," says William Isaacs of the Johns Hopkins University Medical Institutions in Baltimore.

Isaacs notes that prostate cancer researchers have also examined genetic variations in the androgen receptor, the cell surface protein that binds to testosterone or DHT and transmits commands into the cell. A few recent studies suggest that black men often have a shorter than normal form of the receptor gene, which may change how prostate cells with the receptors respond to androgens.

This genetic variation also seems to increase the prostate cancer risk of black men and may even predispose them to more aggressive forms of the disease, says Issacs. *— J. Travis*

Ant life: It's a sister-eat-brother world

The battle between the sexes takes a particularly uncivil twist in the ant world, normally considered a shining example of cooperation. If the sex ratio in their communities fails to work to their genetic advantage, female ants adjust the balance, presumably by killing males, a new study reveals.

Like every good mother, the queen of an ant colony favors neither her sons nor her daughters. They are both equally related to her, equally capable of passing along her genes, and produced in similar numbers.

Workers, which are female, inherit one set of genes from the queen and one set from the male that fertilized her. Males, however, come from unfertilized eggs and inherit only one set of maternal genes. As a result, on average, the females are genetically more similar to their sisters than to their brothers. Because resources are often scarce, workers may somehow adjust the colonies' sex ratio to boost the well-being of their sisters, increasing the likelihood that more of their genes get passed on, researchers have speculated.

The degree to which colony members are related to each other varies according to the mating habits of the queen. Workers in a group whose queen had more than one mate are less genetically similar to each other than those whose queen had a single partner. The offspring of a single father therefore have a greater interest in boosting their sisters' chances of survival. Studies have shown that female offspring dominate single-father colonies but not the other colonies.

"However, these studies did not demonstrate whether workers indeed manipulated sex ratios," Liselotte Sundström, a biologist at the University of Helsinki in Finland, and her colleagues assert in the Nov. 8 SCIENCE.

In their experiments, the scientists determined the sex of almost 3,000 eggs from 59 colonies of wood ants (*Formica exsecta*) living on Finnish islands. Almost all of the colonies had only one queen. About 60 percent of the queens had mated with just one male; the rest carried the sperm of at least two partners.

All the colonies had roughly equal numbers of male and female eggs. However, the groups whose queens had only one mate showed a high ratio of female to male adults, indicating that something happened to the male eggs or larvae. In the laboratory, additional eggs disappear when placed in a nest with female ants, says Sundström.

The loss of males in the colonies "can best be explained by workers selectively neglecting or destroying males," the team argues.

The study will greatly sharpen interest in how workers determine both the sex of larvae and their own genetic similarity to their sisters, notes Jon Seger, an evolutionary biologist at the University of Utah in Salt Lake City, in an accompanying comment. The results "get us closer to understanding the mechanisms of sex ratio manipulation," he adds.

Sundström acknowledges that at this point, scientists have no evidence of how workers might distinguish male from female eggs. Chemicals on the surface of the eggs may tip them off, she speculates.

She and her colleagues are now investigating how other factors, such as a colony's size, influence the sex ratio. Before killing off the males, workers determine whether they can raise enough females to make up for the drop in population, she suspects. *— T. Adler*