

Teams implicate new gene in prostate cancer

This summer, prostate cancer forced New York City Mayor Rudolph W. Giuliani to drop out of a heated race for the U.S. Senate. That political bombshell brought new attention to a disease that ranks as the most common cancer among U.S. men and kills more than 30,000 of them annually.

Despite intensive study of the cancer, in which cells of the walnut-shaped prostate gland proliferate wildly, researchers have had little success identifying genes that underlie the disease. This week, however, Myriad Genetics of Salt Lake City announced that its scientists have found a mutated gene in a few families whose men are prone to prostate cancer.

"There have been a lot of attempts to find [hereditary] prostate cancer genes in the past . . . but no one has ever identified one until now," says Timothy Rebbeck of the University of Pennsylvania School of Medicine in Philadelphia.

Only about 10 percent of men diagnosed with prostate cancer have a family history of the disease, and it's unclear how many of these hereditary cases can be explained by mutations in the newfound gene. Suggesting a role for the gene in the general male population, Rebbeck and the Myriad scientists also have preliminary evidence that a relatively common variant of the gene may increase the prostate cancer risk of the many men who harbor it.

At this week's American Society of Human Genetics meeting in Philadelphia, Rebbeck and Myriad's Sean Tavtigian both are scheduled to report studies connecting the newly discovered gene to prostate cancer. The Myriad investigators unearthed the gene through DNA analyses of large Mormon families in Utah that maintain detailed genealogical records. In a few families with many members having prostate cancer, Tavtigian and his colleagues identified a gene that's mutated in men with the disease but not in those free of the cancer.

The discovery of this new gene has surprised prostate cancer researchers. "This is one we didn't have any hints about," says Elaine Ostrander of the Fred Hutchinson Cancer Research Center in Seattle.

"Because we may be able to learn something about the biology of this gene and its effect on prostate cancer, we may be able to develop new preventions or therapies," adds Rebbeck.

Scientists don't know the function of the gene or its protein, although certain features of the protein suggest that it may bind to and even repair DNA. Many disparate species, including fungi, have the gene, indicating that it plays a general but vital role in cells, says Rebbeck.

In the families studied by Myriad, mutations prevent the gene's production of a functional protein. The Myriad team has also found that the gene can contain more subtle changes, so-called polymorphisms, that may influence its activity or its protein's shape.

Among a sample of men, the Myriad scientists found that one polymorphism occurred more often in those men diagnosed with prostate cancer than in those without the disease. Myriad then asked Rebbeck to examine the gene in a larger population of men with and without prostate cancer.

Rebbeck, too, found that the suspect form of the gene turns up more frequently in men with the disease. His group's initial analysis, reported in the October *AMERICAN JOURNAL OF HUMAN GENETICS*, suggests that having this particular gene variant more than doubles a man's risk of developing prostate cancer.

Until many more men are studied, it's too early to say with any confidence how this gene influences prostate cancer susceptibility of men in general, cautions John Witte of Case Western Reserve University School of Medicine in Cleveland.

"Prostate cancer is so complicated that the question is, how many more [such genes] are

there going to be?” says Witte. “Is this one a grand slam or a single?” He predicts that several other prostate cancer genes will soon be found.

—*J. Travis*