A team led by Harvard researchers has found dramatic genetic links to prostate cancer that appear to underlie many of the cases and help explain the higher occurrence of the disease among African-American men.

The scientists said yesterday that they have identified a set of changes in human DNA that are common in the American population and that, together, can increase the risk of the disease by more than five times. These changes may be responsible for up to two-thirds of African-American cases and one-third of the cases among Caucasian-Americans, according to a report in the journal Nature Genetics.

The discovery may eventually allow doctors to improve screening, a strategy that has had an impact on the disease, by identifying high-risk people to be tested at an earlier age. And it could someday lead to better treatments for the second-leading cancer killer of men.

The finding also poses a compelling mystery. All the dangerous genetic changes identified lie in stretches of DNA that contain no genes and have no known biological function. This, researchers said, suggests that scientists are now on the trail of a new mechanism behind cancer, and it raises the possibility that this mechanism is behind some other forms of cancer.

"It is a smoking gun to something new," said Dr. Tom Hudson, who was not involved in the research and is president and scientific director of the Ontario Institute for Cancer Research in Toronto. "It is very exciting."

The field of prostate cancer genetics is moving rapidly. Last year, deCODE Genetics, a company in Iceland, identified the first genetic variant, a portion of DNA that is different from the rest of the population's, which is associated with a 60 percent increase in risk of prostate cancer. The new work, led by David Reich of Harvard Medical School, identified five variants. These six variants, as well as another one already found, are more common in Americans with African ancestors than those with European ancestors, Reich said.

The study suggests that genetics are a powerful reason for African-Americans' greater susceptibility to prostate cancer. African-Americans are 56 percent more likely to get the disease than Caucasian men, and 2 1/2 times more likely to die of it, according to the Prostate Cancer Foundation in Santa Monica, Calif.

Reich cautioned, however, that scientists could not tell from the research how much the genetic variants contribute to the disparity in the incidence or death rate of the disease. Other factors, including genetic changes that have not been identified and the environment, may play a role in the disease's higher incidence among African-Americans.

The new variants were identified by studying the DNA of 7,500 people, some of whom had prostate cancer. The research team focused on a particular region on chromosome 8, which previous research, including the deCODE work, has implicated in the disease. They looked for DNA variants that victims of prostate cancer tended to have, but healthy people did not.

DeCODE also published research yesterday, in the journal Nature Genetics, that confirmed one of the variants found by the Reich team. A third paper by researchers at the National Cancer Institute, also published yesterday, confirmed another of the variants.

Doctors cautioned that the work was too preliminary to have any immediate implications for patients. A genetic test based on the new research could help identify patients at greater risk of cancer, but it would not indicate who was going to get the disease.

Once researchers feel they have a better grasp of the genetics behind the disease, they will need to do a prospective study, gathering large numbers of people and then following them to see how useful the genetic data would be in helping doctors decide who should get screening tests or particular treatments, according to Janet L. Stanford, a biologist at the Fred Hutchinson Cancer Research Center in Seattle.
Another issue is that doctors do not have good drugs for halting the progress of prostate cancer, according to Dr. Pier Paolo Pandolfi, a prostate cancer researcher at the Memorial Sloan-Kettering Cancer Center in New York. Having such drugs would make information about a person’s future risk more useful, Pandolfi said, because the highest-risk group could be treated before people have symptoms.

The research may eventually lead biologists to such treatments, said Pandolfi and other scientists. Today, the cause of prostate cancer is a mystery, so it is difficult to find ways of attacking it. The new research provides insight into the disease, though biologists said the results were puzzling because the genetic variants linked to prostate cancer do not lie within a gene.

Genes are stretches of DNA that instruct cells to create certain proteins, which are the machinery and building blocks of all life, from bacteria to humans. Many of the genetic causes of diseases discovered until now have been mutations in genes, which lead cells to make defective proteins or to make too little or too much of a protein.

In this case, however, it is not clear how the genetic variations cause the biological changes that lead to cancer. All of the variants are found near a gene that is known to be overactive in prostate cancer tumors, so it is possible that the variants cause some change in how that gene functions. Or, biologists said, perhaps something else is happening.

“Right now we are completely in the dark,” said Pandolfi. “But it is only when you raise the questions that you can look for answers.”

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Abstract (Document Summary)

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