Biomarkers and Prostate Cancer Progression

By Mike Fillon

An international team of researchers believe they may have found, if not the smoking gun, at least a few DNA “bullets” that determine whether prostate cancer will become aggressive.

A new biomarker study, which appeared in the Aug. 16, 2011, online edition of Cancer Epidemiology, Biomarkers, and Prevention, identified five inherited genetic variants associated with aggressive prostate cancer. The five single-nucleotide polymorphisms (SNPs) were located in five genes—one each—that may affect prostate cancer progression, according to the study’s authors, who say this study is the first population-based study to show that germline genetic variants predict prostate cancer–specific survival.

The researchers focused on markers that could offer prognostic information after diagnosis. “Our goal was to identify a panel of markers that are easily measured from the man’s genetic background that would indicate the likelihood that he’s going to have an aggressive course of his disease or not,” said study co-author Janet L. Stanford, Ph.D., co-director of the Fred Hutchinson Cancer Research Center’s Program in Prostate Cancer Research and a member of its Public Health Sciences Division. “This could help those men and their physicians better manage that prostate cancer and guide their treatment recommendation.”

Stanford said their ultimate goal is to develop a blood test that could be done in the clinic that would yield more accurate predictions than current tools(261,597),(738,695).

According to Paul G. Corn, M.D., Ph.D., of the Department of Genitourinary Medical Oncology at the University of Texas M.D. Anderson Cancer Center in Houston, the study “illustrates the power of molecular biology in creating opportunities for personalized therapy in patients newly diagnosed with prostate cancer. This information will greatly help guide clinicians and patients in deciding how aggressively to treat a particular patient’s tumor.”

What They Did

Researchers based at the National Cancer Institute–funded Pacific Northwest Prostate Cancer Specialized Program in Research Excellence genotyped 937 SNPs in 156 candidate genes they believed would be potentially important in prostate cancer progression. From that initial panel of genes, they selected specific genetic variants, which they genotyped after examining biopsy results from a population-based cohort of 1,309 prostate cancer patients in Seattle who were aged 35 to 74 years at diagnosis.
“From that cohort, we identified 22 individual SNP markers that were strongly associated with death from metastatic prostate cancer in our population,” said Stanford.

They then took the 22 SNPs to colleagues at the Karolinska Institutet in Stockholm and Umea University in Umea, Sweden. The Swedish researchers genotyped the same 22 SNPs in another population-based group of 2,875 prostate cancer patients in Sweden in the same age group as their American counterparts. Two SNPs failed genotyping in the Swedish population, and five of the remaining 20 SNPs were validated as being statistically significantly associated with death from prostate cancer.

The five SNPs included the following:

1. **LEPR (or LEP-R).** LEP-R was the strongest marker associated with prostate cancer mortality. It functions as a receptor for the fat cell–specific hormone leptin and helps control tissue growth, inflammation, blood vessel development, and bone density. Stanford said LEPR is an interesting candidate for understanding disease progression, because the primary metastatic site for prostate cancer is bone and is fatal.

2. **RNASEL.** RNASEL is associated with inherited prostate cancer. It is associated with apoptosis (programmed cell death), inflammation, and cell proliferation, a feature of cancer cells.

3. **Interleukin 4 (IL-4).** The IL-4 gene stimulates the immune system to develop mast cells, resting T cells, and activated B cells. IL-4 is associated with tumor growth, blood vessel development, and cancer cell migration.

4. **Cryptochrome 1 (CRY1).** CRY1 affects circadian rhythm and may affect androgen levels, which are involved in prostate cancer progression.

5. **Armadillo Repeat gene deleted in velo-cardio-facial syndrome (ARVCF).** ARVCF is a member of the catenin family of proteins, which play an important role in the formation of adherens junction complexes, believed to facilitate communication between the inside and outside of cells. Stanford said increased expression of ARVCF disrupts cell adhesion, which may facilitate cancer progression.

Stanford said that men in the study who carried four or all five of these genetic markers had a 50% higher risk of dying from their prostate cancer than patients who had two or fewer.

**Not So Fast . . .**

Having this type of genetic information at hand may be particularly beneficial for understanding such a heterogeneous disease whose progression may take place over several years. When the disease is first diagnosed, clinicians face the problem of what treatment to recommend, because they don’t fully understand how to predict how aggressive the tumor will become.

Because the course of the disease is unpredictable, men who have indolent, slow-growing tumors are often overtreated. At the other end of the spectrum are undertreated men, who have more aggressive disease and don’t know it, and postpone aggressive therapy.

Although current early detection guidelines from organizations including the National Cancer Center Network and the American Urological Association recommend biopsies for elevated or a rapid rise in prostate-specific antigen (PSA), a recent study found that change in PSA levels over time, known as PSA velocity, is a poor predictor of prostate cancer that often leads to unnecessary biopsies.

The study, published in the Feb. 24 issue of the Journal, included more than 5,000 men and found no evidence that men with a high PSA velocity should undergo biopsies in the absence of other indications. “In other words, if a man’s PSA has risen rapidly in recent years, there is no cause for concern if his total PSA level is still low and his clinical exam is normal,” said lead author Andrew Vickers, Ph.D., an associate attending research methodologist in the department of epidemiology and biostatistics at the Memorial Sloan-Kettering Cancer Center in New York.

But this conclusion doesn’t solve the underlying problem: who should be treated aggressively and who can afford watchful waiting.

**More Research Needed**

The current biomarker study bumps the issue a bit forward, Vickers said, explaining that researchers have long struggled to actually find germline mutations in prostate cancer that affect its aggressiveness. “It’s very nice to see we’ve finally identified some genes that actually do predict aggressive prostate cancer,” Vickers said.

Still, further study is needed, Vickers added. “They’ve provided very strong evidence of their hypothesis, which is that certain germline mutations lead to aggressive prostate cancer,” he said. “However, the size of that effect is actually very small, and that’s why I doubt the clinical value at this time. I doubt that anytime soon, we’re going to be giving gene tests to prostate cancer patients.”

Shuji Ogino, M.D., Ph.D., at the Dana-Farber Cancer Institute in Boston, agreed that the study is an important step in understanding prostate cancer but that the researchers need to go further. “While this is an advance, a large piece is missing,” he said. “Tumor molecular features need to be considered in this context of germline variants.”

For now, Stanford said her team at Fred Hutchinson is now seeking additional cohorts—including those with fatal events and patients undergoing a variety of treatments—to test all 22 SNPs to validate the original five and to see whether others emerge as more statistically significant.

“We are working very hard to try and find better biomarkers that would help distinguish different subsets of patients,” she said. “That would be beneficial for helping patients make decisions about treatments, and for physicians to make better recommendations about treatments.”