Researchers map genome of advanced, lethal prostate cancers and discover 'hypermutation'

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A team of researchers at Fred Hutchinson Cancer Research Center and the University of Washington has conducted the first comprehensive assessment of every gene in the genome of advanced, lethal prostate cancer. Until now, the genetic composition of such tumors had been poorly defined.

In the process, they have discovered a number of potential key drivers – recurrent genetic mistakes – common to advanced prostate cancer that may contribute to disease progression. The researchers also have identified several instances of genetic "hypermutation," a gross excess of single-letter DNA "spelling errors" that could cause the cancer to become resistant to therapies commonly used to slow the progression of advanced prostate cancer, such as androgen-blocking drugs and surgical castration.

Corresponding authors Peter S. Nelson, M.D., a member of the Hutchinson Center's Human Biology Division, and Jay Shendure, M.D., Ph.D., an associate professor of Genome Sciences at UW and an affiliate member of the Hutchinson Center's Human Biology Division, and colleagues report their findings Sept. 26 in the *Proceedings of the National Academy of Sciences* Early Edition. The lead author of the paper was Akash Kumar, a graduate student in Genome Sciences and an M.D.-Ph.D. candidate at UW.

"The most interesting finding to come out of our DNA sequencing project was the discovery of three aggressive tumor types that had 10 times the number of mutations compared to the other advanced prostate cancers we studied," Nelson said. "That was very surprising and unusual. We don't know the cause of these hypermutated tumors, but the frequency of the mutations suggests these tumors might evolve very rapidly to develop resistance to therapies."

The discovery of these genetic mutations should provide clues that illuminate why some prostate cancers are lethal, and potentially could be used to develop screening tests for early detection or drug targets to slow or halt cancer growth, Nelson said.

"The mutations underlying the progression of prostate cancer to an advanced state have been understudied to date," Shendure said. "Although further work is certainly necessary, our hope is that identifying the genes in which these mutations occur will facilitate biological insights and the development of new therapeutic strategies."

For the study, the researchers determined the mutational status of 23 aggressive and lethal, drug-resistant human prostate cancers, including those that had metastasized, or spread, beyond their primary site of origin and those that had not. They used a technology called exome sequencing to survey the mutational landscape. This method is more efficient and cost-effective than whole-genome sequencing because it zeroes in on just 1 percent of the human genome – the exome – a highly functional region that harbors the majority of disease-causing mutations.

In aggressive tumors, the researchers identified a number of genes with recurrent germline (inheritable) or somatic (noninheritable) mutations, including variants in TP53, a gene that encodes tumor protein p53, which normally functions as a tumor suppressor; and GPC6, a gene that encodes glypican-6, which regulates cell growth and division. They also

found recurrent mutations in several genes whose mechanisms in prostate cancer development are not yet well understood, as well as thousands of individual, or "personal," mutations unique to individual tumors.

The researchers also found that of nearly 90 mutations associated with tumors that are resistant to testosterone suppression – a common treatment for advanced prostate cancer – each tumor studied had at least one mutation in the Wnt signaling pathway, a network of proteins known to play a variety of important roles in embryonic development and cancer, among other things.

Nelson and researchers at the Hutchinson Center contributed to the concepts underlying the study and confirmed the identified mutations using alternate technologies. Shendure and colleagues at the UW provided key tissue samples and a majority of the exome sequencing and analysis, among other contributions.

Provided by Fred Hutchinson Cancer Research Center