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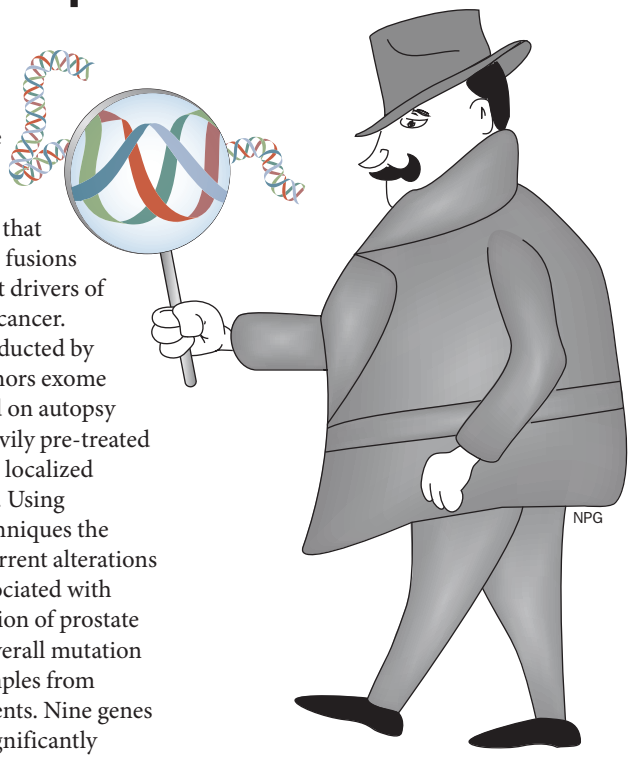
UROLOGICAL CANCER

Genetic landscape studies of prostate cancer offer new clues



Prostate cancer is the second most common cancer in men and one of the leading causes of cancer death. Unfortunately, many men are subjected to overtreatment of indolent disease, which is associated with a high morbidity. Although localized prostate cancer can be highly treatable, metastatic disease kills more than 32,000 men in the USA each year. Treatment with androgen-deprivation therapy can produce rapid responses in men with metastatic disease, but almost all patients relapse and eventually develop castration-resistant prostate cancer (CRPC).

Understanding the genetic landscape of this disease would not only shed light on disease progression but potentially help in the development of new therapies. Now, two studies using exome sequencing approaches, one published in *Nature*, and the other in *Nature Genetics*, have provided novel insights into the genetic basis of advanced-stage disease that also define a new subtype of prostate cancer.

Levi Garraway and coauthors analyzed the coding regions of 112 prostate tumours and matched normal tissue samples from treatment-naive men who had undergone prostatectomy. The researchers identified 5,764 somatic DNA mutations in tumour samples that were absent from normal tissue. A more in-depth analysis of recurrent somatic mutations revealed 12 genes that were highly expressed in tumour samples that were not previously known to be altered in prostate cancer: these included *FOXA1*, *MED12*, *THSD7B, SCN11A* and *ZNF595*. The most frequently mutated gene among localized and advanced-stage prostate cancer samples was *SPOP,* which was mutated at a frequency of 6–15% across multiple independent cohorts. The mutations in *SPOP* affected residues involved in the substrate-binding cleft; therefore, of significant biological consequence. Interestingly, all exomes with *SPOP* mutations lacked the *ETS* family gene rearrangements across multiple independent patient cohorts, indicating that *SPOP* and *ETS* family gene fusions represent early and distinct drivers of carcinogenesis in prostate cancer.

In the second study, conducted by Kenneth Pienta and coauthors exome sequencing was performed on autopsy samples from 50 lethal heavily pre-treated CRPCs, and 11 high-grade localized untreated prostate cancers. Using integrative sequencing techniques the researchers identified recurrent alterations that were known to be associated with development and progression of prostate cancer. Surprisingly, the overall mutation rates were low, even in samples from heavily treated CRPC patients. Nine genes were identified as being significantly mutated in the samples analyzed, and three of these genes were newly identified as having a role in this disease (namely *MLL2, OR5L1* and *CDK12*).

Pienta's team focused on genes with recurrent high-level gains or losses or genes with global copy number changes. They found deletions and mutations in *CHD1*, which encodes a chromatin-remodelling enzyme. Mutations in other genes controlling chromatin and histone modification were also revealed, including *MLL2*. Immunoprecipitation and RNA interference experiments showed MLL2 was associated with the androgen receptor (AR). Proteins that physically interact with the AR, such as FOXA1 were also mutated. FOXA1 was shown to inhibit AR signalling and increase tumour growth in cell line experiments and xenograft models, thereby demonstrating a novel mechanism of AR signalling. Pienta explains, "we identified several 'driver' mutations and copy number alterations in both known and novel pathways and genes, including identification of *MLL2* and *CDK12* as new significantly mutated genes. These represent new targets for therapeutic development."

In the future, Pienta's team plans "to use these studies as a basis and rationale for studying serial biopsies on patients with metastatic prostate cancer as they undergo therapy. This has provided preliminary data for the recently awarded SU2C grant in prostate cancer, which will create a cohort of 500 CRPC patients who will undergo serial integrative sequencing as they progress through therapies." Collectively, these studies help define the mutational landscape of patients with CRPC, identify novel mechanisms of AR signalling, and reveal a distinct new molecular subtype of prostate cancer.

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Original articles Barbieri, C. E. *et al*. Exome sequencing identifies recurrent SPOP, FOXA1 and MED12 mutations in prostate cancer. *Nat. Genet.* doi:10.1038/ng.2279 | Grasso, C. S. *et al*. The mutational landscape of lethal castration-resistant prostate cancer. *Nature* doi:10.1038/nature11125