Prostate cancer is diagnosed in more than 200,000 men and accounts for more than 30,000 fatalities in the USA every year [1]. The course of this disease is remarkably heterogeneous; some cancers remain asymptomatic for decades, while others rapidly metastasize to bone and other tissues, resulting in substantial morbidity and mortality. Although several genetic abnormalities have previously been identified in prostate cancer, including recurrent rearrangements involving the androgen-regulated serine protease gene $\text{TMPRSS2}$ and members of the $\text{ETS}$ family of oncogenic transcription factors [1], a complete view of the prostate cancer genome has been lacking.

Relatively few point mutations in prostate cancer
Berger et al. [1] sequenced the genomes of seven high-grade aggressive primary prostate cancers and corresponding normal tissues by generating approximately 30-fold genome coverage of paired-end, short-read sequencing on the Illumina platform. After mapping reads to the human reference genome, they found that each cancer genome possessed on average less than one somatic point mutation per megabase. This mutation rate is far lower than that previously seen in genomes of lung cancer and melanoma (Table 1), but similar to that reported for breast cancer and acute myelogenous leukemia [2,3,5]. This pattern supports the notion that the mechanisms underlying the genesis of prostate cancer do not include common environmental carcinogens, such as UV radiation in melanoma or tobacco exposure in lung cancer, which result in DNA point mutations. The tumors had an average of 20 non-synonymous (protein-changing) substitutions per genome. Despite this relatively low mutation frequency, two genes, $\text{SPTA1}$ and $\text{SPOP}$, were recurrently mutated. $\text{SPOP}$ has been shown to interact with a cell-death-associated protein Daxx, and $\text{SPTA1}$ encodes a scaffold protein involved in determining cell morphology. The specific mechanism by which these genes influence tumorigenesis remains to be established. Additionally, genes encoding proteins involved in chromatin remodeling, antigen processing and heat shock were enriched for mutations, suggesting that these pathways may be relevant in prostate tumorigenesis.
Table 1. Genome alterations reported in published whole genome studies

| Tumor type          | Number of tumors sequenced | Approximate number of point mutations per tumor | Average number of non-synonymous mutations per tumor | Number of rearrangements per tumor | Reference(s) |
|---------------------|----------------------------|-----------------------------------------------|-----------------------------------------------------|-----------------------------------|--------------|
| Lung (non-small-cell)  | 1                          | 50,000                                        | 302                                                 | 43                                | Lee et al. (2010) [8] |
| Melanoma            | 1                          | 30,000                                        | 187                                                 | 74                                | Pleasance et al. (2010) [2] |
| Lung (small-cell)    | 1                          | 20,000                                        | 94                                                  | 58                                | Pleasance et al. (2010) [3] |
| Breast              | 2                          | 6,000                                         | ~30                                                 | 40                                | Ding et al. (2010) [4]; Shah et al. (2009) [9] |
| Prostate            | 7                          | 4,000                                         | 20                                                  | ~100                              | Berger et al. (2011) [1] |
| AML                 | 1                          | 1,000                                         | 8                                                   | ND                                | Mardis et al. (2009) [5] |

AML, acute myelogenous leukemia; ND, not determined.

A larger role for rearrangements

Perhaps the most striking finding of the study by Berger et al. [1] concerned chromosomal alterations. Each cancer genome contained an average of 100 inter- and intrachromosomal rearrangements. Unsurprisingly, three tumors contained rearrangements involving TMPRSS2 and ERG (ETS-related gene) - an event previously reported to occur in approximately 50% of primary prostate carcinomas [6]. Of great interest, the investigators reported that a subset of rearrangements participated in a ‘closed chain’ pattern in which multiple inter- and intrachromosomal locations exchange breakpoint arms without any loss in total genetic material (Figure 1). This pattern is distinct from one in which all breaks occur as reciprocal pairs, and the authors hypothesized that these events may be due to the simultaneous disruption of many co-localized chromosomes through a mechanism depicted in Figure 1. Genomic insults such as genotoxic damage produced by oxidative stress or ionizing radiation can induce DNA breaks. Subsequent reshuffling of chromosomal material may help to drive the derangement of many genes in parallel, the importance of which is bolstered by the recent findings of ‘chromothripsis’ or chromosomal ‘shattering’ in other tumor types [7]. In contrast to the events seen in chromothripsis, the rearrangements seen in these prostate cancers affected multiple chromosomes at once. This pattern of rearrangement suggests a unique mechanism of tumorigenesis within prostate cancer that may be associated with the known influences of androgen receptors and other regulators of gene expression.

A potential mechanism for rearrangements in hormone-driven cancers

It was noted by Berger et al. that closed chain rearrangements could occur if chromosomes were spatially co-localized before rearrangement; this phenomenon has been seen to occur through androgen receptor-induced ‘transcription hubs’ that approximate intra- and intergenic regions under common regulatory control (Figure 1). The investigators looked for a correlation between the locations of breakpoints and specific chromatin marks in a similar TMPRSS2-ERG fusion-positive prostate cancer cell line and found a significant association between rearrangements in some TMPRSS2-ERG fusion-positive tumors and open chromatin marks within the cell line [1].

In contrast, tumors without TMPRSS2-ERG alterations demonstrated an inverse correlation between open chromatin and rearrangements, indicating that these tumors either possess different patterns of chromatin organization from that of the cell line or preferentially rearrange in regions of closed chromatin [1]. Directly exploring chromatin structure in these and additional prostate tumors, and measuring the overlap between rearrangement breakpoints and chromatin state may address this question.

Interestingly, Berger et al. [1] found that associations between open chromatin and rearrangements also extended to breast cancer. Of 18 previously sequenced breast cancer samples, 16 exhibited rearrangements that overlapped significantly with open chromatin regions in the prostate cancer cell line as well as with estrogen receptor binding sites. This pattern was not observed in lung cancers or melanoma, suggesting that it may be most relevant to hormone-driven cancers, such as breast and prostate cancers, which involve nuclear hormone receptors.

Candidate genes identified by whole genome sequencing

Whole genome sequencing also identified a set of novel genes recurrently disrupted by rearrangements [1]. CADM2, encoding a cellular adhesion molecule, was rearranged in three out of seven tumors studied and rearrangements were seen in an additional six out of ninety prostate cancers using fluorescence in situ hybridization; as some rearrangements are too complex to resolve via the fluorescence in situ hybridization method, this number is likely to be an underestimate. Similarly, the gene MAGI2 was recurrently affected by a copy-neutral rearrangement. MAGI2 is predicted to be
involved in the phosphatidylinositol 3-kinase pathway based on known interactions with PTEN. Additionally, mutations in PTEN and MAGI2 within the seven genomes appear to be mutually exclusive, further suggesting the involvement of the phosphatidylinositol 3-kinase pathway as a driver of prostate carcinogenesis and a potentially important therapeutic target. As pointed out by the investigators, the fact that MAGI2 was disrupted in a copy-neutral manner would likely make it invisible to detection methods other than whole genome sequencing.

**Implications for future prostate cancer research and treatment**

The analysis of prostate cancer genomes highlights the utility of whole genome sequencing as a discovery tool in cancer. Berger *et al.* uncovered novel candidate onco-genes using this approach, identified a new pattern of chromosomal rearrangement and provided insights into the mechanisms by which rearrangements may arise. As the search for additional tumor-promoting and tumor-suppressing genes continues, this work exemplifies the power of detailed genomic characterization to identify genes disrupted by rearrangements that remain undetectable by other approaches.

Additional genomic studies of prostate cancers are needed before its landscape and mechanisms of tumorigenesis can be said to be well understood. The finding that TMPRSS2 fusion status appears to influence a tumor’s pattern of chromosomal rearrangement is interesting. It will be important to characterize the chromatin state of fusion-negative cells to help resolve the question of whether rearrangements in prostate cells have a tendency to occur in regions of open chromatin. Sequencing other types of tumors can determine whether the closed-chain patterns of rearrangements are present in other hormonally driven cancers or rather are unique to the prostate. In this regard, a comparison of estrogen-receptor-positive and estrogen-receptor-negative breast cancers may be informative. The Berger *et al.* study was not sufficiently large to rule out the possibility of new recurrently mutated genes in prostate cancers, and examining the genomes of additional tumor samples, especially metastases, may uncover new therapeutic targets. However, the data do suggest that few specific genes will be mutated at high frequency in primary prostate cancers, and support the concept of pathway-based analyses that involve assessing alterations in multiple genes that each may influence the activation state of a given network. Lastly, it will be important to establish the functional relevance of both rearrangements and point mutations identified through cause-effect experiments in preclinical models of prostate cancer.

The future of cancer management will likely be governed by partitioning tumors into categories or classes based on their constellation of mutations, structural alterations and epigenetic states that control oncogenic pathways. Of critical clinical utility will be those genomic features that are prognostic and those that are amenable to pharmacological control. In the simplest case, large subtypes of cancers are driven by single gene alterations that are directly targetable, such as the Bcr-abl fusion protein of chronic myelogenous leukemia, and others where mutations in a particular pathway are common, but do not represent the single accelerator of tumor growth, such as *EGFR* mutations in subsets of lung cancer. More likely, as emphasized by whole genome analyses of epithelial tumors, cancers such as those arising in the prostate are influenced by a collection of relatively rare mutations. Clinical assessment of tumors in this scenario will require methods to comprehensively assess their genomes in order to prescribe the most appropriate therapeutics. The diversity and complexity of tumor genomes coupled with the increasing affordability...
and utility of the whole genome sequencing approaches indicate that these technologies will be increasingly used and have an important future in the management of cancer patients.

Abbreviations
AML, acute myelogenous leukemia; Daxo, death-domain associated protein; ERG, ETS related gene; ER, estrogen receptor; PI3K, phosphatidylinositol 3-kinase pathway.

Competing interests
The authors declare that they have no competing interests.

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