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RESEARCH HIGHLIGHT

Highlights from the prostate cancer genome report

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Prostate cancer (CaP) is the second most frequently diagnosed cancer of men worldwide (899 000 new cases, 13.6% of the total), with nearly 75% of the registered cases occurring in developed countries (644 000 cases).[1] Blood prostate-specific antigen test has revolutionized the early detection of CaP and organ-confined CaP is effectively managed by state-of-the-art treatments including radical prostatectomy or radiation therapy.[2] In the past decade, tremendous progress has also been made in our understanding of the biology and common genomic alterations in CaP.[3,4] New molecular marker assays have promise in improving CaP diagnosis.[5–8] Despite these advances, major challenges remain with our ability to distinguish indolent cancers from the more aggressive cancers detected early due to widely used prostate-specific antigen test. Furthermore, development of molecular stratification of CaP for targeted and more effective therapies is critically needed.

Berger *et al.*[9] in *Nature* reported the whole genome sequence of prostate tumors by comparing DNA from primary prostate tumor with matched blood (as control) from seven patients (stage T2c or greater, and Gleason grade 7 or higher). Of the seven tumor specimens, three were *TMPRSS2–ERG*-positive and four were *TMPRSS2–ERG*-negative. Each specimen was sequenced by paired-end, massively parallel sequencing at 30-fold mean sequence coverage (the average number of times a base is read).

The authors reported a median of 3866 point mutations in each tumor, at a frequency of about one mutation per megabase, which is comparable to acute myeloid leukemia and breast cancer[10,11] but about 10-fold lower than rates reported for small-cell lung cancer and melanoma.[12,13] The mutation rate at cytosine-phosphate-guanosine dinucleotides was more than 10-fold higher than that at all other genomic positions. Twenty non-synonymous base mutations were identified per sample within protein-coding genes. Six insertion or deletions (indels) were found in coding region of the tumor suppressor gene, *PTEN* (phosphatase and tensin homolog). Three of seven tumors harbored either mutations in the chromatin modifiers (*CHD1*, *CHD5* and *HDAC9*) or in members of the heat shock protein-1 heat shock stress response chaperone complex (*HSPA2*, *HSPA5* and *HSP90AB1*). The paucity of well-recognized cancer mutations (p53, RB, RAS, EGFR, PI3K and RAF) in this study supports the literature on primary CaP.[3,4,14]

In contrast to the relatively low number of somatic point mutations, this study uncovered a high number of complex genomic rearrangements (median of 90 in each prostate tumor) in which relatively large fragments of inter- and intrachromosomal DNA were exchanged. These translocations/rearrangements generated a mix of chimeric chromosomes containing chains of balanced or 'copy-neutral' translocations with remarkable conservation of the overall genetic material. Of the 594 rearrangements, 78% were validated by multiplexed PCR followed by massively parallel sequencing events. While *TMPRSS2–ERG* fusions were confirmed in expected specimens, two other genes that had not been previously associated with CaP, *CSMD3* and *cell adhesion molecule 2* (*CADM2*) were rearranged in three out of seven tumors. Furthermore, four of the seven tumors harbored recurring genomic rearrangements disrupting either *PTEN* (chromosome loss), a prostate tumor suppressor, or *MAGI2* (balanced translocations), a membrane-associated guanylate kinase and a *PTEN*-interacting protein not previously implicated in prostate tumorigenesis. Mutations to one or both *PTEN* and *MAGI2* genes may deregulate the PI3 kinase pathway and contribute towards cancer progression. Authors provide some explanation for the observed translocations by suggesting that break points may associate with hormonally modulated open chromatin regions in *TMPRSS2–ERG* positive tumors, whereas other mechanisms may be involved in rearrangements associating with ETS fusion negative prostate tumors. Intriguingly, this study noted a similar association of open chromatin with sites of somatic rearrangement in another hormone-driven cancer, breast cancer.

In summary, this is a ground breaking study of prostate cancer genome. The new observations on a large number of balanced translocations/rearrangements are intriguing. The frequencies of new rearrangements involving *CSMD3* and *CADM2* or mutations of chromatin modifiers or heat shock response genes need further evaluations. This study confirms widely studied oncogenic activation of the *ERG* gene or inactivation of the *PTEN* tumor suppressor in primary CaP. These data and previous studies affirm promising potential of these pathways in CaP therapeutic targeting. Future studies of CaP genomes with defined cohorts have potential to unravel novel biomarkers and therapeutic targets.

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1 Jemal A, Center MM, DeSantis C, Ward EM. Global patterns of cancer incidence and mortality rates and trends. *Cancer Epidemiol Biomarkers Prev* 2010; **19**: 1893–907.
2 Walsh PC, DeWeese TL, Eisenberger MA. Clinical practice. Localized prostate cancer. *N Engl J Med* 2007; **357**: 2696–705.
3 De Marzo AM, Nelson WG, Bieberich CJ, Yegnasubramanian S. Prostate cancer: new answers prompt new questions regarding cell of origin. *Nat Rev Urol* 2010; **7**: 650–2.
4 Kumar-Sinha C, Tomlins SA, Chinnaiyan AM. Recurrent gene fusions in prostate cancer. *Nat Rev Cancer* 2008; **8**: 497–511.
5 Makarov DV, Loeb S, Getzenberg RH, Partin AW. Biomarkers for prostate cancer. *Annu Rev Med* 2009; **60**: 139–51.

6 Lee GL, Dobi A, Srivastava S. Prostate cancer: diagnostic performance of the PCA3 urine test. *Nat Rev Urol* 2011; **8**: 123–4.
7 Laxman B, Morris DS, Yu J, Siddiqui J, Cao J *et al*. A first-generation multiplex biomarker analysis of urine for the early detection of prostate cancer. *Cancer Res* 2008; **68**: 645–9.
8 Rice KR, Chen Y, Ali A, Whitman EJ, Blase A *et al*. Evaluation of the ETS-related gene mRNA in urine for the detection of prostate cancer. *Clin Cancer Res* 2010; **16**: 1572–6.
9 Berger MF, Lawrence MS, Demichelis F, Drier Y, Cibulskis K *et al*. The genomic complexity of primary human prostate cancer. *Nature* 2011; **470**: 214–20.
10 Ley TJ, Mardis ER, Ding L, Fulton B, McLellan MD *et al*. DNA sequencing of a cytogenetically normal acute myeloid leukaemia genome. *Nature* 2008; **456**: 66–72.
11 Ding L, Ellis MJ, Li S, Larson DE, Chen K *et al*. Genome remodelling in a basal-like breast cancer metastasis and xenograft. *Nature* 2010; **464**: 999–1005.
12 Berger MF, Levin JZ, Vijayendran K, Sivachenko A, Adiconis X *et al*. Integrative analysis of the melanoma transcriptome. *Genome Res* 2010; **20**: 413–27.
13 Pleasance ED, Stephens PJ, O'Meara S, McBride DJ, Meynert A *et al*. A small-cell lung cancer genome with complex signatures of tobacco exposure. *Nature* 2010; **463**: 184–90.
14 Palanisamy N, Ateeq B, Kalyana-Sundaram S, Pflueger D, Ramnarayanan K *et al*. Rearrangements of the RAF kinase pathway in prostate cancer, gastric cancer and melanoma. *Nat Med* 2010; **16**: 793–8.