TP53 structural variants in metastatic prostatic carcinoma

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Abstract

Sequencing data have been instrumental in identifying oncogenic drivers in prostatic carcinoma and highlighting biomarkers that define aggressive disease. A review of a series of 30 primary and metastatic prostatic carcinomas clinically sequenced at our cancer genomics laboratory utilizing a targeted gene panel identified recurrent structural variants in the TP53 gene. These structural variants were found in 27% of all sequenced cases and represented 36% of the cases with metastatic disease. TP53 structural rearrangements have been previously reported in a significant subset of osteosarcomas, where they result in loss of p53 protein expression by immunohistochemistry. Similarly, in our prostate cases with TP53 structural rearrangements for which tissue was available for testing, we find loss of p53 protein expression by immunohistochemistry. In the eight TP53-rearranged cases, concurrent PTEN loss was identified in 4 cases, TMPRSS2-ERG fusion in 5 cases, and AR and FOXA1 amplification in 1 case each. Our results from this small case series suggest that TP53 rearrangements with loss of expression represent a frequent alternative mechanism of inactivation of this key tumor suppressor gene with potential utility as a marker of aggressive disease. Recognition of this TP53 rearrangement pathway is essential to accurately identify prostatic carcinomas with loss of TP53 function.

Introduction

Prostate cancer is the second most common cancer in men worldwide [1]. The heterogeneous clinical behavior of prostatic carcinoma complicates treatment decisions and highlights the need for accurate predictors of aggressive disease. Sequencing of primary prostate carcinomas and castration resistant prostate carcinomas have identified recurrent molecular alterations, including ETS family transcription factor fusions; mutations in SPOP, FOXA1, and TP53; PTEN loss; and AR amplification [2, 3]. Some of these alterations, including TP53 mutations, are associated with aggressive clinical behavior [4–7].

The function of the p53 protein can be disrupted through a variety of mechanisms, including missense mutations and homozygous loss of the gene locus. Recently, inactivating
structural rearrangements involving intron 1 of the TP53 gene were identified in many pediatric osteosarcomas [8]. Subsequent application of a FISH assay to examine TP53 intron 1 rearrangements in a wide variety of tumor types suggested that such rearrangements are specific to osteosarcoma [9]. Importantly, these structural variants are not detected by many TP53 mutation assays, and as a result, it is likely that many osteosarcomas previously considered TP53 wild-type may in fact be TP53 mutant [8]. Such misclassification may confound studies examining the impact of TP53 inactivation on tumor aggressiveness in any tumor type.

Here, based on a small series of cases that underwent targeted clinical sequencing, we report that TP53 structural rearrangements are frequent in metastatic prostatic carcinoma.

Materials and methods
Structural variants of TP53 gene with breakpoints in intron 1 identified in successive cases of prostatic carcinomas prompted a retrospective review of all tumor cases clinically sequenced at University of California, San Francisco (UCSF), with an aim to identify the distribution of pathogenic TP53 structural variants across different tumor types and specificity for any tumor types. The study was conducted under an IRB (IRB protocol number 15–15823) approved by the University of California San Francisco Human Research Protection Program. Form of consent was not obtained in accordance with the waiver deemed appropriate by IRB as the the data was analyzed anonymously with no more than minimal risk to the subjects. Clinical cases of solid and hematopoietic tumors that included 926 tumors submitted for sequencing over a period of 2 years from 2015 to 2017 were reviewed. Further, we reviewed all TP53 alterations identified across all cases of prostate carcinomas sequenced. Additional clinical information including sample source, treatment modalities and disease progression to metastatic disease for prostate carcinomas were tabulated. Metastatic designation was defined in accordance with 8th Edition AJCC staging manual and did not include regional lymph node involvement.

Matched normal and tumor tissues were sequenced in all cases. Capture-based next-generation sequencing was performed at the UCSF Clinical Cancer Genomics Laboratory, using an assay (UCSF500 panel) that targets the coding regions of 479 cancer-related genes, select introns from approximately 40 genes, and the TERT promoter with a total sequencing footprint of 2.8 Mb as previously described [10]. Structural variants were identified by Delly and Pindel, with verification using the Integrative Genomics Viewer (IGV). All cases were screened specifically for TP53 gene alterations including missense mutations, small insertions or deletions, copy number changes and structural variants. Specifically, the TP53 gene being the most frequently mutated gene in cancers is very well covered by the panel, targeting all coding exons and intron 1, with the exception of two small regions of intron 1 where coverage dips below an average of 10x, chr17:7,584,200–7,585,100 (~900 bp) and chr17:7,581,630–7,581,790 (~160 bp), hg19 coordinates. In addition, due to their small size and proximity to targeted exons, introns 2, 4, 5, 6, 7, and 8 are also covered (Fig 1).

Immunohistochemistry for p53 was performed on all cases with available paraffin blocks using standard CLIA-compliant protocols. Immunohistochemical results were broken into 3 categories: overexpression when there was strong nuclear positivity in greater than 90% cells, negative when there was no detectable nuclear staining or wild type when there was variable patchy nuclear staining.

Results
We retrospectively reviewed 926 solid and hematopoietic tumors that were submitted for clinical sequencing over a 2-year period to specifically identify cases with structural variants in TP53 gene. In all, structural variants involving TP53 gene were identified in 19 cases (2%).
These included 8 out of 30 (26.6%) prostate carcinomas, 5 out of 5 (100%) of osteosarcomas, and 1 or 2 cases of 6 other tumor types (Table 1). While in 12 of these cases, the structural variant identified was a translocation, in the remaining 7 cases, the structural variants were

Table 1. Distribution of TP53 fusions across different types.

| Tumor type                                           | cBioportal data (11,12) | Current study |
|------------------------------------------------------|-------------------------|---------------|
| Adenocarcinoma, NOS                                  | 20% (1/5)               | 0% (0/35)     |
| Anaplastic astrocytoma                               | 0% (0/141)              | 5% (1/19)     |
| Anaplastic thyroid carcinoma                         | 3% (1/33)               | 0% (0/2)      |
| Urothelial carcinoma                                 | 0.1% (2/1862)           | 7% (1/14)     |
| Breast Invasive Ductal Carcinoma                     | 0.03% (2/6205)          | 0% (0/11)     |
| Cholangiocarcinoma                                   | 0.6% (1/150)            | 0% (0/5)      |
| Colorectal Adenocarcinoma                            | 0.2% (7/3365)           | 5.7% (2/35)   |
| Cutaneous Melanoma                                   | 0.1% (1/977)            | 0% (0/33)     |
| Leiomyosarcoma                                        | 2% (4/205)              | 0% (0/1)      |
| Lung Adenocarcinoma                                  | 0.08% (3/3524)          | 0% (0/10)     |
| Lung Squamous Cell Carcinoma                         | 0.06% (1/1694)          | 0% (0/1)      |
| Mixed Germ Cell Tumor                                | 1.5% (1/63)             | 0% (0/2)      |
| Myxofibrosarcoma                                     | 6% (3/50)               | 0% (0/0)      |
| Oligoastrocytoma                                     | 0.36% (1/277)           | 0% (0/2)      |
| Osteosarcoma                                          | 6.9% (3/43)             | 100% (5/5)    |
| Prostate Adenocarcinoma                              | 0.57% (24/4180)         | 26.6% (8/30)  |
| Metastatic Prostate Carcinoma                        | 1.27% (14/1095)         | 33.3% (8/22)  |
| Renal Clear Cell Carcinoma                           | 0.06% (1/1734)          | 0% (0/20)     |
| Salivary Carcinoma                                   | 0.37% (1/270)           | 0% (0/2)      |
| Serous Ovarian Cancer                                | 0.06% (1/1754)          | 4% (1/25)     |
| Stomach Adenocarcinoma                               | 0.07% (2/2994)          | 0% (0/7)      |
| Undifferentiated Pleomorphic Sarcoma/Malignant Fibrous Histiocytoma/High-Grade Spindle Cell Sarcoma | 4% (4/999)               | 100% (1/1)   |
| Uterine Leiomyosarcoma                                | 1.75% (1/57)            | 0% (0/2)      |
inversions or interstitial deletions. The breakpoints for these variants predominantly involved intron 1 (N = 13) (Fig 2A), and in remaining cases were distributed across exon 1 (N = 2), intron 2 (N = 1), intron 5 (N = 1) and intron 10 (N = 2).

Of the 926 samples submitted for sequencing, 30 samples were of prostatic carcinoma on which sequencing was performed on primary (N = 15) and metastatic (N = 15) tumor samples and were obtained from patients with metastatic (N = 22) and localized (N = 8) disease. For one case (#15) sequencing was performed separately on both primary and metastatic samples. Of the 15 patients with metastatic samples sequenced, 13 had received radiation therapy, androgen deprivation therapy, and/or chemotherapy, while of the 15 patients with sampling of primary carcinoma, 5 had received radiation therapy, androgen deprivation therapy, and/or chemotherapy. Neuroendocrine features were seen in 2 metastatic carcinoma samples and in 1 primary carcinoma sample. TP53 gene alterations were identified in 15 of 30 (50%) cases, with 6 of these cases demonstrating missense variants or small insertions/deletions, 8 cases demonstrating structural variants, and 1 case demonstrating homozygous deletion of the gene (Table 2). Of the 15 prostate cancers with TP53 mutations of any kind, 13 of them had either known metastatic disease at sequencing, or metastatic disease was identified at subsequent follow up. In contrast, of the 15 cases that were TP53 wild type, 9 had metastatic disease at the
time of sequencing or metastatic disease was identified at subsequent follow up; while 6 remained without evidence of metastatic disease on follow up (Table 3). In agreement with prior studies, this suggests that TP53 disruption is associated with more aggressive disease. However, because our study is a clinical study selected for aggressive tumors, statistical analysis across clinical parameters such as primary and metastatic disease, treatment modalities, tumor grade and histology is not performed. Of note, in one case, we sequenced both the primary and metastatic tumors, and only the metastatic tumor demonstrated the TP53 rearrangement.

The structural variants in 8 cases of prostatic carcinoma included breakpoints in intron 1 (N = 5), intron 2 (N = 1), exon 1 (N = 1) and intron 10 of TP53 (Fig 2) and are predicted to result in loss of gene expression. Amongst the structural variants, 5 were translocations with different fusion partners (namely DNAH2 (2 cases), HDAC9, PACS1 and TMEM107) while 3 were inversions (Table 4). Additionally, 2 of the cases had concurrent exon 1 deletions.

Immunohistochemical analysis for p53 protein expression was done for 15 cases with available blocks; these included 3 cases with structural variants (all metastatic carcinomas), 3 with pathogenic missense variants (1 primary, 2 metastatic carcinomas), and 9 with no detectable TP53 alterations (4 primary, 5 metastatic carcinomas). As expected, all 3 cases with structural variants showed a complete absence of detectable nuclear staining, consistent with loss of protein expression, while the 3 cases with pathogenic missense variants showed strong nuclear positivity in more than 90% of the cells. In the 9 cases lacking detectable TP53 alterations, the staining ranged from 5 to 50% with variable nuclear staining intensity (Fig 3).

| Case # | TP53 alterations | Treatment history | Histologic Features and metastatic site | Sample sequenced | Follow up disease status |
|--------|-----------------|-------------------|----------------------------------------|-----------------|------------------------|
| 1      | TP53 p.F109V    | No treatment      | Prostate carcinoma, Gleason 4+5, (pelvic lymph nodes) | P               | P                      |
| 2      | TP53 p.F134L    | ADT + Radiotherapy| Metastatic prostate carcinoma (spine, liver) | M               | M                      |
| 3      | TP53 p.G334V    | ADT + Chemotherapy + Radiotherapy | Prostate carcinoma with neuroendocrine features (bone) | M               | M                      |
| 4      | TP53 p.R196delinsQHLIR | No treatment | Metastatic prostate carcinoma (liver, lung, bone) | M               | M                      |
| 5      | TP53 p.R273C    | ADT               | Prostate carcinoma, Gleason 5+5, (pelvic lymph nodes) | P               | P                      |
| 6      | TP53 p.Y236C    | ADT + Chemotherapy | Metastatic prostate carcinoma (liver, bone) | M               | M                      |
| 7      | TP53 CNV       | ADT + Radiotherapy + Proton beam therapy | Prostate carcinoma extending into bladder (rectosigmoid colon) | M               | M                      |
| 8      | TP53 5’ deletion including exon 1, TP53 rearrangement | ADT + Chemotherapy + Radiotherapy | Metastatic prostate carcinoma (bone) | M               | M                      |
| 9      | TP53 rearrangement, intron 2 | ADT + Radiotherapy | Metastatic neuroendocrine prostate carcinoma (skin, liver, lung) | M               | M                      |
| 10     | TP53 rearrangement | No treatment | Metastatic prostate carcinoma (bone) | M               | M                      |
| 11     | TP53 pericentric inversion | No treatment | Metastatic prostate carcinoma (bone) | P               | M                      |
| 12     | TP53 rearrangement | ADT | Prostate carcinoma, Gleason 4+5 (bone) | P               | M                      |
| 13     | TP53 rearrangement exon 1 | No treatment | Prostate carcinoma, Gleason to 4+5 (distant lymph nodes, bone) | P               | M                      |
| 14     | TP53 structural rearrangement with focal deletion | No treatment | Metastatic poorly differentiated neuroendocrine prostate carcinoma (liver) | P               | M                      |
| 15     | TP53 structural rearrangement with focal deletion | ADT + Chemotherapy | Prostate carcinoma with treatment effect (bone) | P               | M                      |

Abbreviations: ADT- androgen deprivation therapy, M- metastatic, P- primary.

https://doi.org/10.1371/journal.pone.0218618.t002
Other genetic alterations identified in cases with structural variants (all metastatic carcinomas) included TMPRSS2-ERG fusions in 5 of 8 cases, PTEN copy number loss in 4 of 8 cases (homozygous deletion of the entire gene in 3 cases and 18-bp deletion of intron 1 case), and AR and FOXA1 amplification in 1 of 8 cases each. Of the 7 prostatic carcinomas with missense mutations, small insertions/deletions and copy number changes in TP53, TMPRSS2-ERG fusion was seen in 4 cases, PTEN mutations/ copy number loss in 3 and AR amplification in 1.

**Discussion**

The TP53 tumor suppressor gene is amongst the most frequently mutated genes in human cancers. Most mutations in TP53 are single nucleotide variants or small insertions/deletions resulting in missense, nonsense, truncating, splice site and frameshift alterations [11, 12]. Structural variants have been reported much less frequently in osteosarcomas, prostate carcinomas, small cell lung cancer [8, 9, 13–16, 17] and more recently on deep whole genome analysis of castrate resistant metastatic prostate carcinomas [18]. Here, based on a small series of

| Case # | Type of Structural Variants | TP53 Breakpoint | Partner Gene |
|--------|----------------------------|-----------------|--------------|
| 8      | TP53 translocation and 5’ deletion including exon 1 | Intron 1 | DNAH2 (Chr 17) intron 40 |
|        |                             | Exon 1 deletion | Not applicable |
| 9      | TP53 inversion              | Intron 2 | Intergenic |
| 10     | TP53 pericentric inversion  | Intron 1 | Upstream of CRX8 |
| 11     | TP53 rearrangement          | Intron 1 | TMEM107 (Chr 17) exon 3 |
| 12     | TP53 rearrangement          | Intron 1 | DNAH2 |
| 13     | TP53 rearrangement          | Exon 1 | PACS1 |
| 14     | TP53 structural rearrangement with focal exon 1 deletion | Intron 1 | HDAC9 (Chr 7) intron 11 |
|        |                             | Focal exon 1 deletion | Not applicable |
| 15     | TP53 inversion              | Intron 10s | Intergenic |

Abbreviations: ADT- androgen deprivation therapy, M- metastatic, P- primary.

https://doi.org/10.1371/journal.pone.0218618.t003

https://doi.org/10.1371/journal.pone.0218618.t004
cases undergoing targeted sequencing for clinical purposes, we have shown that TP53 structural rearrangements are an unexpectedly common cause of TP53 inactivation in advanced prostatic carcinomas.

TP53 structural rearrangements involving intron 1 were initially reported in the context of osteosarcomas [15, 16]. More recently, using whole genome analysis of 52 osteosarcoma samples, Chen et al [8] found clonal TP53 structural variants in 55% of cases, 90% of which had breakpoints in intron 1. TP53 structural variants have also been reported in osteosarcoma cell lines [15], rare instances in myeloid leukemia [18, 19] and blast crisis in chronic myelogenous leukemia [20], and in the germline of some families with Li-Fraumeni syndrome [9]. FISH analysis of 215 osteosarcomas using probes directed at the TP53 gene found biallelic structural rearrangements in 11% of cases [9]. In contrast, the FISH test did not identify TP53 structural rearrangements in other 124 bone forming tumors and tumor like lesions or in 966 other tumor samples, including 33 prostatic adenocarcinomas. Based on these FISH results, the authors suggested that such TP53 intron 1 rearrangements may be specific to osteosarcomas. However, in their study, the authors did not provide additional details of whether these were primary or metastatic prostate carcinomas and the tumor grade that could account for the differences in detection from the current study.

In contrast, our data suggests that in addition to osteosarcoma, inactivating TP53 rearrangements involving intron 1 are quite common in prostatic carcinoma. We identified TP53 structural variants in 8 of 30 (27%) prostatic carcinomas. While these structural variants were seen in primary and metastatic tumor samples, all cases progressed to metastatic disease. Thus, 36% (8/22) of the patients with metastatic disease in this small cohort demonstrated TP53 inactivation through structural rearrangement. Most frequently the breakpoint occurred in intron 1, similar to prior reports in osteosarcomas [9] and prostatic carcinomas [14], with a few breakpoints elsewhere in the gene. The immunohistochemical expression of p53 protein also correlated with underlying molecular alterations as also demonstrated in other studies. Both high levels of expression or complete absence of staining have been shown to correlate with mutant TP53 status [21–23], suggesting the use of the immunohistochemical stain as a good marker for mutant status of the gene, although the staining pattern is not specific for the mutation type. Pathogenic mutations in TP53 result in either loss of p53 expression or its ability to bind to DNA response elements. A subset of TP53 mutations result in gain of oncogenic function or mutations with dominant negative effect with accumulation of mutant protein at high

![Fig 3. p53 immunohistochemical expression pattern in prostate carcinomas with TP53 alterations. A- Diffuse nuclear positivity (> 90%) is seen in a case with TP53 p.R273C mutation (10x). B- TP53 structural rearrangement resulting in complete loss of TP53 expression. Staining of background stromal cells and inflammatory cells seen as an internal control (20x). C- Prostate carcinoma with wild type TP53 showing weak and patchy (less than 5%) nuclear staining (20x).](https://doi.org/10.1371/journal.pone.0218618.g003)
levels [24] and some of these have also been associated with development of chemoresistance [25].

In general agreement with our findings, examination of the cBioportal database [11, 12] demonstrates TP53 fusions in 68 out of 65,690 samples queried (0.1%), including 24 of 4365 samples (0.6%) of prostatic carcinomas from 4180 patients (accessed 8/14/2018), with prostate carcinomas being the most common tumor type with TP53 fusions (24/68) (Table 1). Specifically in the metastatic prostate carcinomas, TP53 fusions were reported in 14 of 1095 cases (1.27%). The fusions were distributed across 10 primary prostatic carcinomas and 14 metastatic prostatic carcinomas. PTEN alterations, TMPRSS2-ERG rearrangement, AR alterations and FOXA1 mutations were identified in 7, 17, 8 and 3 of the 24 cases respectively. The TP53 rearrangements reported in cBioportal are intragenic fusions or translocations, all involving different fusion partners. There may be several reasons for the lower rate of detection of TP53 fusions in cBioportal database including potentially different grades of tumors analyzed, intronic coverage that could be significantly less on whole genome or whole exome sequencing as compared to more targeted sequencing for clinical assays, and lack of bioinformatic support for detection of these alterations.

Recently whole genome analysis of 57 primary prostatic carcinomas and transcriptome sequencing of 20 primary prostate carcinomas [13] identified numerous interdependent translocations and deletions occurring through a process of concurrent disruption of several genes in a coordinated manner that the authors termed chromoplexy. Resultant gene disruptions involved spatially separated genes as well as genes in the same pathway, affecting multiple cancer genes. Oncogenic genes with recurring deletions or rearrangements in their study [13] included PTEN (N = 9), NKK3-1 (N = 8), CDKN1B (N = 3), TP53 (N = 4) and RB1 (N = 2). Clonal evaluation of altered genes led to a proposed oncogenic model of cancer progression initiated by deletion of NKK3-1 or FOXP1 and TMPRSS2-ERG fusion, followed by CDKN1B or TP53 alterations and finally ending in PTEN loss. More recently, deep whole genome analysis of castrate resistant metastatic prostate carcinoma also identified structural variants in tumor suppressor genes including TP53, PTEN, RB1, CDKN1B and CHD1 resulting in biallelic gene inactivation, novel gene fusions and tandem gene duplications. In this analysis, biallelic inactivation of CDK12, BRCA2 and TP53 strongly correlated with the structural variants and chromothripsis [18].

The higher percentage of TP53 structural variants found in our study may be a reflection of the small study size and relatively high percentage of metastatic tumors in our cohort. Tumors chosen for sequencing tend to be aggressive in nature, as a frequent goal of sequencing is to find additional targetable alterations in advanced cases. It is unclear if TP53 rearrangements will be found in any significant number in lower grade organ confined disease. We recommend prospective studies to evaluate for distribution of TP53 structural variants in primary and metastatic prostatic carcinomas, which might serve as a marker of aggressive disease and disease progression when detected.

The primary limitation of our study is its small size, which limits our ability to determine the clinical significance of the TP53 rearrangements identified. Moreover, the limited sampling could lead to over or underrepresentation of the various TP53 alterations identified in our cohort.

**Conclusion**

In this small series, we report the occurrence of TP53 structural variants in a significant subset of metastatic prostatic carcinomas that underwent targeted sequencing for clinical purposes. Recognition of this alternative mechanism of TP53 loss of function is important to properly
characterize the genetics of prostatic carcinomas for both clinical and research purposes, as some assays will not detect these structural rearrangements. Our findings need to be validated in a larger cohort of metastatic prostate carcinomas.

**Author Contributions**

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**References**

1. Brawley OW. Prostate cancer epidemiology in the United States. World J Urol. 2012; 30:195–200. [PMID: 22476558]
2. Grasso CS, Wu YM, Robinson DR, Cao X, Dhanasekaran SM, Khan AP et al. The mutational landscape of lethal castration-resistant prostate cancer. Nature. 2012; 487:239–43. [PMID: 22722839]
3. Cancer Genome Atlas Research Network. The Molecular Taxonomy of Primary Prostate Cancer. Cell. 2015; 163:1011–25. [PMID: 26544944]
4. Guedes LB, Almutairi F, Haffner MC, Rajoria G, Liu Z, Klimek S et al. Analytic, Preanalytic, and Clinical Validation of p53 IHC for Detection of *TP53* Missense Mutation in Prostate Cancer. Clin Cancer Res. 2017; 23:4693–703. [PMID: 28446506]
5. Kluth M, Harasimowicz S, Burkhardt L, Grupp K, Krohn A, Prien K et al. Clinical significance of different types of p53 gene alteration in surgically treated prostate cancer. Int J Cancer. 2014; 135:1369–80. [PMID: 24523142]
6. Schlomm T, Iwers L, Kirstein P, Jessen B, Kollermann J, Minner S et al. Clinical significance of p53 alterations in surgically treated prostate cancers. Mod Pathol. 2008; 21:1371–8. [PMID: 18552821]
7. Stricker HJ, Jay JK, Linden MD, Tamboli P, Amin MB. Determining prognosis of clinically localized prostate cancer by immunohistochemical detection of mutant p53. Urology. 1996; 47:366–9. [PMID: 8633403]
8. Chen X, Bahrami A, Pappo A, Easton J, Dalton J, Hedlund E et al. St. Jude Children's Research Hospital–Washington University Pediatric Cancer Genome Project. Recurrent somatic structural variations contribute to tumorigenesis in pediatric osteosarcoma. Cell Rep. 2014; 7:104–12. [PMID: 24703847]
9. Ribi S, Baumann D, Lee K, Edison, Teo AS, Madan B et al. TP53 Intron 1 hotspot rearrangements are specific to sporadic osteosarcoma and can cause Li-Fraumeni syndrome. Oncotarget. 2015; 6:7727–40. [PMID: 25762628]
10. Kline CN, Joseph NM, Grenert JP, Talevich E, Onodera C, Aboian M et al. Targeted next-generation sequencing of pediatric neuro-oncology patients improves diagnosis, identifies pathogenic germline mutations, and directs targeted therapy. Neuro Oncol. 2017; 19:699–709. [PMID: 28437343]
11. Gao J, Aksoy BA, Dogrusoz U, Dresdner G, Gross B, Sumer SO et al. Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal. Sci Signal. 2013; 6:pl1. [PMID: 23550210]
12. Cerami E, Gao J, Dogrusoz U, Gross BE, Sumer SO, Aksoy BA et al. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. Cancer Discov. 2012; 2:401–4. [PMID: 22588677]
13. Baca SC, Prandi D, Lawrence MS, Mosquera JM, Romanel A, Drier Y et al. Punctuated evolution of prostate cancer genomes. Cell. 2013; 153:666–77. https://doi.org/10.1016/j.cell.2013.03.021 PMID: 23622249

14. Berger MF, Lawrence MS, Demichelis F, Drier Y, Cibulskis K, Sivachenko AY et al. The genomic complexity of primary human prostate cancer. Nature. 2011; 470:214–20. https://doi.org/10.1038/nature09744 PMID: 21307934

15. Masuda H, Miller C, Koeffler HP, Battifora H, Cline MJ. Rearrangement of the p53 gene in human osteogenic sarcomas. Proc Natl Acad Sci U S A. 1987; 84:7716–9. https://doi.org/10.1073/pnas.84.21.7716 PMID: 2823272

16. Miller CW, Aslo A, Tsay C, Slamony D, Ishizaki K, Toguchida J et al. Frequency and structure of p53 rearrangements in human osteosarcoma. Cancer Res. 1990; 50:7950–4. PMID: 2253237

17. George J, Lim JS, Jang SJ, Cun Y, Ozretić L, Kong G et al. Comprehensive genomic profiles of small cell lung cancer. Nature. 2015; 524:47–53. https://doi.org/10.1038/nature14664 PMID: 26168399

18. Quigley DA, Dang HX, Zhao SG, Lloyd P, Aggarwal R, Alumkal JJ et al. Genomic Hallmarks and Structural Variation in Metastatic Prostate Cancer. Cell. 2018; 174:758–769. https://doi.org/10.1016/j.cell.2018.06.039 PMID: 30033370

19. Prokocimer M, Shaklai M, Bassat HB, Wolf D, Goldfinger N, Rotter V et al. Expression of p53 in human leukemia and lymphoma. Blood. 1986; 68:113–8. PMID: 3521760

20. Mashal R, Shtalrid M, Talpaz M, Kantarjian H, Smith L, Beran M et al. Rearrangement and expression of p53 in the chronic phase and blast crisis of chronic myelogenous leukemia. Blood. 1990; 75:180–9. PMID: 1967214

21. Havrilesky L, Darcy KM, Hamdan H, Priore RL, Leon J, Bell J et al. Prognostic significance of p53 mutation and p53 overexpression in advanced epithelial ovarian cancer: a Gynecologic Oncology Group Study. J Clin Oncol. 2003; 21(20):3814–25. https://doi.org/10.1200/JCO.2003.11.052 PMID: 14551300

22. Köbel M1, Reuss A, du Bois A, Kommos S, Kommos F, Gao D et al. The biological and clinical value of p53 expression in pelvic high-grade serous carcinomas. J Pathol. 2010; 222(2):191–8. https://doi.org/10.1002/path.2744 PMID: 20629008

23. Cole AJ, Dwight T, Gill AJ, Dickson KA, Zhu Y, Clarkson A et al. Assessing mutant p53 in primary high-grade serous ovarian cancer using immunohistochemistry and massively parallel sequencing. Sci Rep. 2016; 6:26191. https://doi.org/10.1038/srep26191 PMID: 27189670

24. Mandilaras V, Garg S, Cabanero M, Tan Q, Pastrello C, Burnier J et al. TP53 mutations in high grade serous ovarian cancer and impact on clinical outcomes: a comparison of next generation sequencing and bioinformatics analyses. Int J Gynecol Cancer. 2019. [Epub ahead of print].

25. Wong RP, Tsang WP, Chau PY Co NN, Tsang TY, Kwok TT. p53-R273H gains new function in induction of drug resistance through down-regulation of procaspase-3. Mol Cancer Ther. 2007; 6(3):1054–61. https://doi.org/10.1158/1535-7163.MCT-06-0336 PMID: 17363498