Abstract. Background: Androgen deprivation therapy (ADT) is extensively employed in treatment of prostate cancer. Some studies have found increased risk of Alzheimer’s disease and cognitive impairment in patients treated with ADT. Aim: Since the uncertainty about ADT and dementia might relate to the genetics of prostate cancer and Alzheimer’s disease, we used the Cancer Genome Atlas (TCGA) to examine the relationship between genes implicated in Alzheimer’s disease and genes implicated in prostate cancer in men with prostate cancer. Materials and Methods: The genomics of 492 prostate cancer cases in the Genomic Data Commons TCGA Prostate Cancer data set were examined. Results: Alterations (mutation, amplification or deletion) in prostate cancer gene speckle-type POZ protein (SPOP) significantly co-occurred with alterations in Alzheimer’s disease gene bridging integrator-1 (BIN1). Alterations in prostate cancer gene spectrin alpha 1 (SPTA1) significantly co-occurred with alterations in Alzheimer’s disease gene CD2-associated protein (CD2AP) (p<0.001). The presence of somatic mutations (deleterious and missense/in frame) in SPOP disturbs BIN1 gene expression. SPOP and BIN1 RNA expression in 492 prostate cancer specimens was significantly positively correlated (p<0.001). Increased expression of SPOP in 492 cases of prostate cancer was associated with reduced survival (p=0.00275). BIN1 forms part of a network that interacts with the MYC oncogene, which is activated at the earliest phases of prostate cancer and is linked to disease aggressiveness. Men receiving ADT had tumor with a significantly higher Gleason score (p=0.023). Gleason score and BIN1 RNA expression in 499 prostate cancer specimens were significantly correlated (p<0.001). Conclusion: The severity of prostate cancer is determined by the genetics of the tumor itself, possibly at least in part by the interactions of SPOP/BIN1, MYC/BIN1 and SPTA1/CD2AP. Oncologists treats higher grade prostate cancer with more ADT, which serves as a surrogate marker for disease severity. A weakness of our study is that we did not examine Alzheimer’s disease or dementia at all in patients with cancer, only co-occurrence of genetic alterations. Nevertheless, our analysis of TCGA data does not support the idea that ADT causes Alzheimer’s disease or dementia.

Androgen deprivation therapy (ADT) is extensively employed in treating prostate cancer. Yet the risk of impaired cognition or Alzheimer’s disease in men with prostate cancer receiving ADT is uncertain (1). Some studies of prostate cancer and ADT suggest that risk of Alzheimer’s disease is not increased (2-5), although others have found increased risk of Alzheimer’s disease and cognitive impairment (6-8).

The uncertainty about ADT and dementia may be related to the genetics of prostate cancer and Alzheimer’s disease. In the current analysis, we used the Cancer Genome Atlas (TCGA) to examine the relationship between genes implicated in Alzheimer’s disease and genes implicated in prostate cancer in men with prostate cancer.

Materials and Methods

We examined the genomics of prostate cancer in the Genomic Data Commons (GDC) TCGA Prostate Cancer (PRAD) data set and the MSKCC/DFCI data set (9). The Cancer Genome Atlas (TCGA) contains the analysis of over 11,000 tumors from 33 of the most prevalent forms of cancer (10). To access and analyze the data we used:

• UCSF Xena browser, a web-based visual integration and exploration tool for TCGA data, including clinical and phenotypic annotations (11). Gene expression is quantitated as fragments per kilobase of transcript per million mapped reads upper quartile (fpkm-uq), which is an RNA-Seq-based expression normalization method (12).
Table I. Significantly co-occurring alterations in patients with prostate cancer of speckle-type POZ protein (SPOP), spectrin, alpha 1 (SPTA1), androgen receptor (AR), apolipoprotein E (APOE), bridging integrator-1 (BIN1) and CD2-associated protein (CD2AP). The q-value was derived from the Benjamini Hochberg false-discovery rate correction procedure for multiple comparisons.

| Gene     | Alteration present, cases | OR = (A×D)/(B×C) | p-Value | q-Value | Tendency |
|----------|---------------------------|------------------|---------|---------|----------|
| SPOP     | BNI1                      | 425 46 7 11      | >3      | <0.001  | <0.001   | Co-occurrence |
| APOE     | CD2AP                     | 483 2 1 3       | >3      | <0.001  | <0.001   | Co-occurrence |
| SPTA1    | CD2AP                     | 459 26 1 3     | >3      | <0.001  | 0.004    | Co-occurrence |
| SPTA1    | APOE                      | 457 27 3 2     | >3      | 0.03    | 0.114    | Co-occurrence |
| CD2AP    | AR                        | 479 3 6 1     | >3      | 0.056    | 0.169    | Co-occurrence |
| APOE     | AR                        | 478 4 6 1     | >3      | 0.07    | 0.175    | Co-occurrence |
| BIN1     | CD2AP                     | 468 17 3 1     | >3      | 0.14    | 0.299    | Co-occurrence |
| BIN1     | AR                        | 465 17 6 1     | 2.189    | 0.232    | 0.435    | Co-occurrence |
| SPOP     | SPTA1                     | 427 17 2 2     | < -3    | 0.141    | 0.626    | Mutual exclusivity |
| SPOP     | AR                        | 427 57 7 0     | < -3    | 0.537    | 0.732    | Mutual exclusivity |
| SPOP     | APOE                      | 428 57 4 0     | < -3    | 0.608    | 0.75     | Mutual exclusivity |
| SPTA1    | AR                        | 453 29 7 0     | < -3    | 0.65     | 0.75     | Mutual exclusivity |
| SPTA1    | BIN1                      | 443 28 17 1    | < -10.4 | 0.71     | 0.761    | Mutual exclusivity |
| APOE     | BNI1                      | 466 5 18 0     | < -3    | 0.828    | 0.828    | Mutual exclusivity |

*Log2 value.

• Bioportal, a web-based interface that enables integrative analysis of complex cancer genomics and clinical profiles (13).
• PCViz, an open-source web-based network visualization tool that helps users obtain details about genes and their interactions extracted from multiple pathway data resources.
• Simple statistics were calculated to identify patterns of mutual exclusivity or co-occurrence. For a pair of query genes, an odds ratio (OR) is calculated (Eq. 1) that indicates the likelihood that the events in the two genes are mutually exclusive or co-occurrence across the selected cases

\[ OR = \frac{(A \times D)}{(B \times C)} \]  

where A was the number of cases with alteration (i.e., mutated, amplified or deleted) in both genes; B was the number of cases alteration in gene A but not gene B; C was the number of cases alteration in gene B but not gene A; and D was the number of cases without alteration in both genes. Each pair was then assigned to one of three categories indicative of a tendency toward mutual exclusivity, of a tendency toward co-occurrence, or of no association. To determine whether the identified relationship was significant for a gene pair, Fisher’s exact test was performed (13). The p-value was derived from the Benjamini Hochberg false-discovery rate correction procedure for multiple comparisons.

**Results**

Five hundred patients with primary prostate cancer, aged 61±6.8 (mean±SD), were included. Overall, 30% were White, 1.4% African American, and 0.4% Asian; of the remainder, race was not recorded. A total of 97% of cases were prostate adenocarcinoma acinar type. The number of patients with Alzheimer’s disease was unknown.

Co-occurrence analysis (Table I) indicated that alterations in the prostate cancer gene speckle-type POZ protein (SPOP) were found to co-occur significantly with alterations in the Alzheimer’s disease gene bridging integrator 1 (BIN1) (p<0.001, q<0.001). Alterations in the prostate cancer gene spectrin alpha, erythrocytic 1 (SPTA1) significantly co-occurred with alterations in the Alzheimer’s disease gene CD2-associated protein (CD2AP) (p<0.001, q<0.004). These co-occurring alterations indicate that the genes may work in tandem to drive tumor formation and development.

The presence of somatic mutations (deleterious and missense/in frame) in SPOP deranged BNI1 gene expression. SPOP and BNI1 RNA expression in 492 prostate cancer specimens was found to be significantly positively correlated (p<0.001, Figure 1).

Figure 2 shows that BNI1 RNA gene expression [log2 (fpkm-uq+1)] was significantly negatively correlated with Gleason score in 499 prostate cancer specimens.

Increased expression of SPOP in 492 prostate cancer cases was associated with significantly reduced survival (p=0.00275).

The mean Gleason score of prostate cancer in patients according to receipt of ADT is shown in Figure 3. In those receiving ADT, tumor had a significantly higher Gleason score (p=0.023).

**Discussion**

The observed co-existing BIN1/SPOP mutations and expression within prostate cancer tissue might simply reflect
tumor-suppressor effects of BIN1 (14). But our finding that BIN1 expression was inversely related to Gleason score might suggest germline BIN1 alterations. Dynamic regulation of the BIN1–Tau interaction is involved in Alzheimer’s disease and a high level of BIN1 expression may be protective (15).

BIN1 forms part of a network that interacts with the MYC oncogene (Figure 4). The MYC family consists of three related human genes; one is c-MYC. The N-terminus of the c-MYC oncoprotein interacts with BIN1, which has features of a tumor suppressor (16). MYC is activated at the earliest phases of prostate cancer and in its position on chr8q24 is linked to prostate cancer aggressiveness (17, 18).

CD2AP, a scaffolding molecule regulating signal transduction and cytoskeletal molecules, is implicated in pathogenesis of Alzheimer’s disease. Several single nucleotide polymorphisms of CD2AP are associated with higher risk for Alzheimer’s disease. mRNA levels of CD2AP were found to be reduced in peripheral lymphocytes of patients with sporadic Alzheimer’s disease (18, 19).

In the largest study of ADT to date, of 154,089 men with prostate cancer, those who underwent ADT had a 14% and
20% greater chance of developing Alzheimer’s disease and of dementia, respectively. Those who received four or fewer doses had a 19% chance of being diagnosed with either condition, while the five to eight dose group reached 28% likelihood of Alzheimer’s disease and 24% of dementia; at eight or more doses, the likelihoods were 24% and 21%, respectively. The study suggests an association between ADT and subsequent dementia but does not investigate possible biological mechanisms of the association. The authors conclude that clinicians need to carefully weigh the long-term risks and benefits of exposure to ADT in patients with a prolonged life expectancy and stratify patients based on dementia risk prior to ADT initiation (8).

Alzheimer’s disease symptoms are usually preceded by a preclinical phase that may be 16 years long (20). We propose that ADT dosage reflects the severity of a preclinical phase that has been underway for years. The severity is related to the genetics of the tumor itself, possibly at least in part by the interactions of SPON/BIN1, MYC/BIN1 and SPTA1/CD2AP. ADT does not appear to cause new cases of Alzheimer’s disease, although we have no actual data on Alzheimer’s disease for the prostate cancer cohort. Higher grade prostate cancer was associated with more ADT (Figure 3), which serves as a surrogate marker for disease severity. In the TCGA data, patients with a higher Gleason score were more likely to receive ADT.

A weakness in our study is that we present somatic mutation data rather than germline data. Co-existing germline mutations would be present in every cell of the body including the brain, where Alzheimer’s disease is manifest. A somatic mutation develops in a specific cell and is then propagated to daughter cells. In our study, the cell with the mutation is in the prostate. We are uncertain whether these same mutations co-exist in the brain.

Nevertheless, the idea that ADT causes Alzheimer’s disease or dementia in men with prostate cancer is certainly in need of further study.

Conflicts of Interest

None.

Authors’ Contributions

Each Author contributed to the planning, conduction, and reporting of the work described in the article, and both are responsible for the overall content as guarantors.

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