Germline \textit{BRCA2} mutation in a case of aggressive prostate cancer accompanied by spinal bulbar muscular atrophy

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Dear Editor,

Spinal and bulbar muscular atrophy (SBMA) or Kennedy’s disease is a rare X-linked, recessive, lower motor neuron disease caused by a CAG repeat expansion within the first exon of the androgen receptor (AR) gene. Instability of the CAG-triplet repeat impacts AR function; therefore, men with SBMA are thought to be at a very low risk of prostate cancer. We previously reported a case of high-risk prostate cancer with SBMA (repeat length 46).\textsuperscript{1} Here, we present the follow-up of this patient along with investigation of his genetic background. The patient was a 54-year-old Japanese man diagnosed with prostatic adenocarcinoma, with a Gleason score of 4 + 5 by prostate needle biopsy at our institute (Keio University Hospital, Tokyo, Japan). Prostate-specific antigen (PSA) concentration was 148.0 ng l\textsuperscript{-1}.\textsuperscript{1} Immunohistochemistry showed AR in the nucleus of prostate cancer cells (Supplementary Figure 1). He exhibited proximal limb weakness, perioral fasciculations, and tongue atrophy since the age of 40 years and had been diagnosed with SBMA by neurologists at our institute. Polymerase chain reaction and Sanger sequencing of its product identified more than 46 CAG repeats in the AR gene. He had a family history of SBMA (his maternal uncle), bladder cancer (his maternal uncle), breast cancer (his sister), lung cancer (his sister), and laryngeal cancer (his father). Magnetic resonance imaging suggested capsular invasion and left internal iliac lymph node metastases. Scintigraphy revealed no obvious bone metastasis. Combined androgen blockade with flutamide and leuprorelin was administered. The patient responded well to this hormonal therapy and the PSA nadir persisted for 8 years. After an increase in PSA level was noted, enzalutamide was begun. After approximately 3 years on enzalutamide, his PSA levels gradually increased and new pleural metastases were detected on computed tomography scan (Figure 1a). Metastatectomy was performed, and pathological findings were consistent with those of prostate adenocarcinoma with small-cell neuroendocrine prostate cancer (NEPC; Figure 1b–1e). He was initiated on carboplatin and etoposide chemotherapy and was administered eleven cycles. He responded well, with a PSA decline from 148.35 ng ml\textsuperscript{-1} to <0.02 ng ml\textsuperscript{-1}, and remains without any evidence of progression at 2 years.

To understand the aggressiveness of the disease in this patient, we analyzed his genetic profile. This study was approved by the Ethics Committee of Keio University Hospital (approval numbers: 20150285 and 20160084). Written informed consent for this study was obtained from the patient. Metastatic tumor tissue of the pleura and a blood sample were submitted for next-generation sequencing (NGS) genomic testing using the NCC OncoPanel test, which detects genetic mutations in 114 genes (Supplementary Table 1). Testing of tumor and blood samples identified a breast cancer gene 2 (\textit{BRCA2}) mutation as a pathogenic variant (c.6952C>T, p.R2318; allele frequency in the blood, 37.1%). Furthermore, a DNA polymerase epsilon catalytic subunit (\textit{POLE}) mutation (c.2275C>T, p.R759C) was detected in the tumor sample as a variant of unknown significance.

SBMA is associated with an elongation of CAG repeats within the AR gene, with repeats ranging from 38 to 62, and these repeats disrupt AR gene function. Therefore, patients with SBMA are considered to be at a low risk for prostate cancer with only a few cases reported in the literature.\textsuperscript{2} Our patient with SBMA presented with an aggressive prostate cancer. We identified germline \textit{BRCA2} mutation which likely contributed to prostate cancer development and progression, despite suppressed AR function by CAG repeats. Notably, the tumor in this patient expressed nuclear AR protein; his PSA level was relatively high; and he responded well to initial androgen deprivation therapy and subsequent enzalutamide. Therefore, prostate cancers that develop in the setting of SBMA are not necessarily AR independent. He subsequently exhibited tumor progression and developed histologic features of NEPC which has been associated with AR independence. Through matched tumor-normal sequencing, we identified two predicted pathogenic alterations of potential clinical relevance involving \textit{BRCA2} (germline) and \textit{POLE} (somatic).

\textit{BRCA2} plays a key role in the homologous recombination (HR) DNA repair pathway. In the nucleus of normal eukaryotic cells,
BRCA2 proteins act with other molecules involved in DNA repair. BRCA2 proteins are located in the nuclear foci formed on DNA strands where replication errors are recognized. BRCA2 protects the stalled replication fork from nucleolytic degradation. BRCA2 also regulates DNA repair protein RAD51 homolog 1 (RAD51) recombinase activity and manages HR DNA repair. Loss of BRCA2 function causes double-strand DNA breaks via inactivation of the HR repair pathway and contributes to cancer development. Germ line BRCA2 mutations are etiological factors for hereditary breast and ovarian cancer syndrome. BRCA2 loss also causes other cancers, such as those of the stomach, pancreas, and prostate. Regarding prostate cancer, the frequency of BRCA2 alteration was reported to be 3.3% in localized cases and 9.3%–13.1% in aggressive and metastatic cases. Germ line BRCA2 variants were identified in 1% prostate cancer cases and 0.2% healthy men in a Japanese cohort. Of note, this is the second reported case of SBMA and aggressive prostate cancer found to have a germline BRCA2 mutation, suggesting that BRCA2 loss trumps the need for highly active AR signaling in prostate cancer pathogenesis. Both our patient and the patient previously reported with SBMA and prostate cancer had a neuroendocrine pathology. Because AR expression was heterogeneous in our case, some clones appeared to acquire androgen-independence potentially because of genomic instability due to BRCA2 mutation. This also has potential therapeutic implications considering that prostate cancer cases with BRCA2 mutations are reported to have higher response rates to platinum-based chemotherapy or poly (ADP-ribose) polymerase (PARP) inhibitor therapy. The long remission with carboplatin in our case and significant response to PARP inhibitor therapy in the other reported case can be associated with their BRCA2 mutation.

Comparative analysis of the clinical presentation of BRCA2-associated prostate cancer between the case previously reported and our case is shown in Supplementary Table 2. Both cases developed metastatic prostate cancer at a young age. Both responded well to platinum-based chemotherapy and lived relatively longer than observed in the general progression of patients with NEPC. Of note, both cases also responded to enzalutamide despite the neuroendocrine pathology. Conteduca et al. attempted the use of a PARP inhibitor, talazoparib, and their case responded well. A PARP inhibitor, olaparib, has just been approved for treating BRCA-associated prostate cancer in Japan; we are currently considering it to treat our patient. Because both patients with SBMA developed aggressive prostate cancer, regular PSA screening is recommended for men with SBMA. In patients with SBMA who are diagnosed with prostate cancer, testing for germline BRCA2 should be considered.

In conclusion, this reported case of aggressive prostate cancer in a patient with SBMA accompanied by a pathogenic germline BRCA2 mutation, likely contributed to prostate cancer initiation and treatment response. Despite predicted disrupted AR function in SBMA, our patient did respond to AR-targeted therapies. Genetic testing should be considered for patients with SBMA and prostate cancer.

AUTHOR CONTRIBUTIONS
H Hongo, TK and MO designed the study. H Hongo and TK provided the study materials. H Hongo, TK, H Hayashi, KN, HN and SM conducted and collected data. H Hongo, TK and HB analyzed and interpreted the data. H Hongo, TK and HB wrote the manuscript. H Hayashi, KN, HN, SM and MO edited the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS
All authors declare no competing interests.

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Supplementary Information is linked to the online version of the paper on the Asian Journal of Andrology website.

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### Supplementary Table 1: A total of 114 genes were examined in National Cancer Center OncoPanel

| Gene  | Mutations and copy number alterations for all exons | Fusions     |
|-------|----------------------------------------------------|-------------|
| ABL1  | CRKL, iDH2, NF1, RAC2                              | ALK         |
| ACTN4 | CREBBP, iGF1R, NFE2L2/Nr12, RAD51C, RAI1/CRAF     | BRAF        |
| AKT1  | CTNNB1, iGF2, NOTCH1                              | AKT2        |
| AKT2  | CUL3, IL7R, NOTCH2, RB1                            | ERBB4       |
| AKT3  | DDR2, JAK1, NOTCH3, RET                            | FGFR2       |
| ALK   | EGFR, JAK2, NRG1, RH0A, FGFR3                      |             |
| APC   | ENO1, JAK3, ROS1, NRG1                            |             |
| ARAF  | EP300, KDM6A/UTX, NTRK1, SETBP1, NTRK1             |             |
| ARID1A| ERBB2/HER2, KEAP1, NTRK2, SETD2, NTRK2             | RET         |
| ARID2 | ERBB3, KIT, NTRK3, SMAD4, PDGFRB                  |             |
| ATM   | ERBB4, KRAS, NTSC2, SMARCA4/BRG1, RET              |             |
| AXIN1 | ESR1/ER, MAP2K1/MEK1, PALB2, SMARCB1, ROS1         |             |
| AXL   | EZH2, MAP2K2/MEK2, PBRM1, SMO                       |             |
| BAP1  | FBXW7, MAP2K4, PDGFR1, STAT3                       |             |
| BPL1  | FGFR1, MAP3K1, PDGFRB, STK11/LKB1                  |             |
| BCL2L11/BIM | FGFR2, MAP3K4, PIK3CA, TP53            |             |
| BRAF  | FGFR3, MDM2, PIK3R1, TSC1                         |             |
| BRCA1 | FGFR4, MDM4, PIK3R2, VHL                          |             |
| BRCA2 | FLT3, MET, POLD1                                  |             |
| CCND1 | GNA11, MLH1, POLE                                  |             |
| CD274/PD-L1 | GNAQ, MTOR, PRKCI                   |             |
| CDK4  | GNAS, MSH2, PTC1                                 |             |
| CDKN2A| HRAS, MYC, PTEN                                  |             |
| CHEK2 | IDH1, MYCN, RAC1                                  |             |

*BRCA2: breast cancer gene 2*

### Supplementary Table 2: Comparison of clinical presentation of breast cancer gene 2-associated prostate cancer accompanied by spinal and bulbar muscular atrophy

| Age (y/o) | PSA at Dx | Pathology at Dx | Metastatic site | Initial treatment | PFS of initial Tx (mo) | PFS of 2nd-line Tx (mo) | Subsequent treatment | Current status | Follow-up duration (mo) |
|-----------|-----------|-----------------|-----------------|-------------------|------------------------|------------------------|----------------------|-----------------|------------------------|
| Conteduca's case | 57 | 53 | AdenoCa with NED | Liver, bones | ADT plus DOC and CARBO | 12 | ENZ | 6 | Talazoparib | Living | 36 |
| Our case | 54 | 148 | AdenoCa, GS 4 + 5 | Pelvic LN | ADT | 97 | ENZ | 35 | CARBO and VP16 | Living | 186 |

*Dx: diagnosis; Tx: treatment; mo: months; AdenoCa: adenocarcinoma; NED: neuroendocrine differentiation; LN: lymph node; ADT: androgen deprivation therapy; DOC: docetaxel; CARBO: carboplatin; ENZ: enzalutamide; PAS: prostate-specific antigen; PFS: progression-free survival; GS: Gleason score*
Supplementary Figure 1: (a) Hematoxylin and eosin staining indicated Gleason score 4 + 5 adenocarcinoma. (b and c) Immunohistochemical staining revealed heterogeneous expression patterns of androgen receptor (b) and PSA (c). (d) Cancer cells did not express synaptophysin. The bar indicates 50 μm. PSA: prostate-specific antigen.