Prospective evaluation of germline genetic testing in prostate cancer screening among Japanese.

Shusuke Akamatsu [1]*, Naoki Terada [2]*, Ryo Takata [3]*, Hidefumi Kinoshita [4], Shingo Yamamoto [5], Yukihide Momozawa [6], Harue Tada [7], Michio Yamamoto [7], Naoki Kawamorita [8], Shintaro Narita [9], Mikio Sugimoto [10], Masahiro Nitta [11], Takahiro Kojima [12], Takahiro Kimura [13], Wataru Obara [3], Toshiyuki Kamoto [2], Hidewaki Nakagawa [14], Osamu Ogawa [1]

1 Department of Urology, Kyoto University Graduate School of Medicine, 2 Department of Urology, Faculty of Medicine, University of Miyazaki, 3 Department of Urology, School of Medicine, Iwate Medical University, 4 Department of Urology and Andrology, Kansai Medical University, 5 Department of Urology, Hyogo College of Medicine, 6 Laboratory for Genotyping Development, RIKEN Center for Integrative Medical Sciences, 7 Department of Biomedical Statistics and Bioinformatics, Kyoto University Graduate School of Medicine, 8 Department of Urology, Tohoku University Graduate School of Medicine, 9 Department of Urology, Akita University Graduate School of Medicine, 10 Department of Urology, Faculty of Medicine, Kagawa University, 11 Department of Urology, Tokai University School of Medicine, 12 Department of Urology, Faculty of Medicine, University of Tsukuba, 13 Department of Urology, Jikei University School of Medicine, 14 Laboratory for Cancer Genomics, RIKEN Center for Integrative Medical Sciences

*These authors contributed equally to this work.

Background: Hereditary component plays a significant role in prostate cancer (PCa) susceptibility. Recent GWAS have identified >150 susceptibility loci for PCa, and rare variants in genes such as *BRCA2* and *HOXB13* have also been reported to be associated with the disease. In the present study, we aimed to prospectively test the clinical utility of a common-variant based polygenic risk score (PRS) and also rare pathogenic variant detection of 8 DNA-damage repair associated genes by target sequencing.

Methods: PCSSNP is a multi-institutional cohort which enrolled patients undergoing prostate needle biopsy for the first time between January 2015 and March 2017. Germline DNA was extracted before biopsy. Genotyping of 16 SNPs associated with PCa identified by a genome-wide association study of Japanese population (Takata R, Nat. Genet, 2010) was performed,

and PRS based on a logistic regression model was calculated (Akamatsu S, Plos One, 2012). In addition, target genome sequencing of 8 DNA-repair associated genes (*ATM, BRCA1/2, BRIP1, CHEK2, NBN, PALB2, HOXB13*) was performed to identify pathogenic variants associated with PCa.

Results: Of the 1335 patients, 777 (58.2%) were diagnosed with PCa. Although PRS was significantly higher in patients with PCa, for the patients with PSA2-10 ng/ml, diagnostic ability of the PRS was only marginally better compared to PSA (AUC 0.61 vs 0.58), and was inferior to PSA density (AUC 0.72). However, the age adjusted odds ratio (OR) for the patients with PRS≧2.5 (6.2% of the cohort) was 4.82, and that for PRS≧2.0 (13.1% of the cohort) was 2.68, which is comparable to the age adjusted OR reported for family history of PCa. Among the patients diagnosed with PCa, those with higher PRS (PRS≧2.0) were significantly younger than those with PRS<2.0 (69.4 ±0.63 vs 70.9 ±0.63, p=0.028). A rare pathogenic variant in a DNA repair gene was detected in 18 (2.32%) of the 777 PCa patients and 9 (1.61%) of the 558 non-PCa patients, respectively. The most frequent gene altered was *BRCA2* (n=11) followed by *HOXB13* (n=6). Overall, tumor stage and Gleason score did not differ significantly by the presence of the pathogenic variants. Interestingly, of the 6 patients with *HOXB13* variants, five were p.Gly132Glu alteration, which was recently identified as a novel pathogenic variant in a large-scale Japanese case-control study, and all of them had PCa. No patient had the previously reported *HOXB13* p.Gly84Glu or p.Gly135Glu variants, suggesting that allele frequency of pathogenic variants differ between ethnic groups.

Conclusions: Our data suggest that even though the utility of PRS is limited in the cohort with known PSA, genetic testing with PRS and target sequencing can identify ~15% of the population with very high risk of PCa who may benefit from early screening.

Conflict of Interest: SA receives research grants from AstraZeneca and Astellas. SA receives honorarium from Janssen, Astellas, Takeda, and Sanofi. NT receives research grant from Astellas. NT receives honorarium from Janssen, Astellas, Takeda, and Sanofi.

Funding Acknowledgements: Japan Agency for Medical Research and Development (AMED), AstraZeneca Externally Sponsored Scientific Research, Takeda Science Foundation