available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Prostate Cancer
Editorial by XXX on pp. x-y of this issue

Whole-genome and Transcriptome Sequencing of Prostate Cancer Identify New Genetic Alterations Driving Disease Progression

Shancheng Ren [a,†], *Gong-Hong Wei* [b,†], *Dongbing Liu* [c,d,†], *Liguo Wang* [e,†], *Yong Hou* [c,d,f,†], *Shida Zhu* [c,d,g], *Lihua Peng* [c,d,h], *Qin Zhang* [b], *Yanbing Cheng* [c,g], *Hong Su* [c,d], *Xiuqing Zhou* [c,d], *Jibin Zhang* [c], *Fuqiang Li* [c,d], *Hancheng Zheng* [c], *Zhikun Zhao* [c,d,i,j], *Changjun Yin* [k,§], *Zengquan He* [c], *Xin Gao* [†], *Haiyen E. Zhau* [m], *Chia-Yi Chu* [m], *Jason Boyang Wu* [m], *Colin Collins* [n], *Stanislav V. Volik* [n], *Robert Bell* [n], *Jiaoti Huang* [o], *Kui Wu* [c,d], *Danfeng Xu* [p], *Dingwei Ye* [q], *Yongwei Yu* [r], *Lianhui Zhu* [a], *Meng Qiao* [a], *Hang-Mao Lee* [b], *Yuehong Yang* [b], *Yasheng Zhu* [a], *Xiaolei Shi* [a], *Rui Chen* [a], *Yang Wang* [r], *Weidong Xu* [a], *Yanqiong Cheng* [a], *Chuanliang Xu* [a], *Xu Gao* [a], *Tie Zhou* [a], *Bo Yang* [a], *Jianguo Hou* [a], *Li Liu* [c], *Zhensheng Zhang* [a], *Yao Zhu* [q], *Chao Qin* [k], *Pengfei Shao* [k], *Jun Pang* [†], *Leland W.K. Chung* [m], *Jianfeng Xu* [f,s], *Chin-Lee Wu* [t], *Weide Zhong* [u], *Xun Xu* [c,d], *Yingrui Li* [c], *Xiuqing Zhang* [c], *Jian Wang* [c,v], *Huanming Yang* [c,v], *Jun Wang* [c,w,x,y], *Haojie Huang* [z,‡], *Yinghao Sun* [a,‡,*]

[a] *Department of Urology, Shanghai Changhai Hospital, Second Military Medical University, Shanghai, China;* [b] *Biocenter Oulu, Faculty of Biochemistry and Molecular Medicine, University of Oulu, Oulu, Finland;* [c] *BGI-Shenzhen, Shenzhen, China;* [d] *China National GeneBank-Shenzhen, BGI-Shenzhen, Shenzhen, China;* [e] *Division of Biomedical Statistics and Informatics, Mayo Clinic College of Medicine, Rochester, MN, USA;* [f] *State Key Laboratory of Genetic Engineering, School of Life Sciences, Fudan University, Shanghai, China;* [g] *Division of Genomics and Bioinformatics, CUHK-BGI Innovation Institute of Trans-Omics, The Chinese University of Hong Kong, Hong Kong, China;* [h] *BGI Education Center, University of Chinese Academy of Sciences, Shenzhen, China;* [i] *School of Biological Science and Medical Engineering, Southeast University, Nanjing, China;* [j] *State Key Laboratory of Bioelectronics, Southeast University, Nanjing, China;* [k] *Department of Urology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China;* [l] *Department of Urology, The Third Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China;* [m] *Uro-Oncology Research Program, Department of Medicine, Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA;* [n] *Vancouver Prostate Centre and Department of Urologic Sciences, University of British Columbia, Vancouver, BC, Canada;* [o] *Department of Pathology and Laboratory Medicine, David Geffen School of Medicine, University of California, Los Angeles, CA, USA;* [p] *Department of Urology, Changzheng Hospital, Second Military Medical University, Shanghai, China;* [q] *Department of Urology, Fudan University Shanghai Cancer Center, Shanghai, China;* [r] *Department of Pathology, Shanghai Changhai Hospital, Second Military Medical University, Shanghai, China;* [s] *Program for Personalized Cancer Care, NorthShore University HealthSystem, Evanston, IL, USA;* [t] *Department of Pathology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA;* [u] *Department of Urology, Guangdong Key Laboratory of Clinical Molecular Medicine and Diagnostics, Guangzhou First People's Hospital, Guangzhou Medical University, Guangzhou, China;* [v] *James D. Watson Institute of Genome Sciences, Hangzhou, China;* [w] *Department of Biology, University of Copenhagen, Copenhagen, Denmark;* [x] *The Novo Nordisk Foundation Center for Basic Metabolic Research, University of Copenhagen, Copenhagen, Denmark;* [y] *King Abdulaziz University, Jeddah, Saudi Arabia;* [z] *Department of Biochemistry and Molecular Biology, Mayo Clinic College of Medicine, Rochester, MN, USA*

[†] These authors contributed equally to this study.
[‡] These authors are cosenior authors.
[§] Deceased.
[*] Corresponding author. Department of Urology, Shanghai Changhai Hospital, Second Military Medical University, Changhai Road 168, Yangpu District, Shanghai 200433, China.
Tel. +86-13601-607755; Fax: +86-21-3505-0006.
E-mail address: sunyhsmmu@126.com (Y. Sun).

http://dx.doi.org/10.1016/j.eururo.2017.08.027
0302-2838/© 2017 Published by Elsevier B.V. on behalf of European Association of Urology.

Please cite this article in press as: Ren S, et al. Whole-genome and Transcriptome Sequencing of Prostate Cancer Identify New Genetic Alterations Driving Disease Progression. Eur Urol (2017), http://dx.doi.org/10.1016/j.eururo.2017.08.027

Article info

Article history:
Accepted August 24, 2017

Associate Editor:
James Catto

Keywords:
Chinese prostate cancer
Whole genome sequencing
RNA-seq
CHD1 deletion
TMPRSS2-ERG fusion
AR coactivator mutation
Clustered deleted tumor suppressor genes
Axon guidance pathway
Prognosis
Personalized medicine

Abstract

Background: Global disparities in prostate cancer (PCa) incidence highlight the urgent need to identify genomic abnormalities in prostate tumors in different ethnic populations including Asian men.
Objective: To systematically explore the genomic complexity and define disease-driven genetic alterations in PCa.
Design, setting, and participants: The study sequenced whole-genome and transcriptome of tumor-benign paired tissues from 65 treatment-naive Chinese PCa patients. Subsequent targeted deep sequencing of 293 PCa-relevant genes was performed in another cohort of 145 prostate tumors.
Outcome measurements and statistical analysis: The genomic alteration landscape in PCa was analyzed using an integrated computational pipeline. Relationships with PCa progression and survival were analyzed using nonparametric test, log-rank, and multivariable Cox regression analyses.
Results and limitations: We demonstrated an association of high frequency of *CHD1* deletion with a low rate of *TMPRSS2-ERG* fusion and relatively high percentage of mutations in androgen receptor upstream activator genes in Chinese patients. We identified five putative clustered deleted tumor suppressor genes and provided experimental and clinical evidence that *PCDH9*, deleted/loss in approximately 23% of tumors, functions as a novel tumor suppressor gene with prognostic potential in PCa. Furthermore, axon guidance pathway genes were frequently deregulated, including gain/amplification of *PLXNA1* gene in approximately 17% of tumors. Functional and clinical data analyses showed that increased expression of *PLXNA1* promoted prostate tumor growth and independently predicted prostate tumor biochemical recurrence, metastasis, and poor survival in multi-institutional cohorts of patients with PCa. A limitation of this study is that other genetic alterations were not experimentally investigated.
Conclusions: There are shared and salient genetic characteristics of PCa in Chinese and Caucasian men. Novel genetic alterations in *PCDH9* and *PLXNA1* were associated with disease progression.
Patient summary: We reported the first large-scale and comprehensive genomic data of prostate cancer from Asian population. Identification of these genetic alterations may help advance prostate cancer diagnosis, prognosis, and treatment.
© 2017 Published by Elsevier B.V. on behalf of European Association of Urology.

1. Introduction

Prostate cancer (PCa) is the second most frequently diagnosed cancer and the fifth leading cause of cancer death in men worldwide [1]. The disparity in PCa incidence and death rate is obvious around the globe. The reported incidence and mortality rate of PCa in Asian countries including China were much lower than in Western nations [1,2], with an estimated 60 300 new cases and 26 600 deaths in Chinese men in 2015 [3]. However, the PCa incidence rate increased rapidly in China with an annual percentage change of 12.6% since 2000 [3]. These findings not only highlight the complexity of genomic abnormalities in PCa, but also stress an urgent need of genome-wide molecular and genetic profiling of prostate tumors from different ethnic groups including Asian men.

Prostate tumors also show highly variable clinical outcomes. Some patients survive for over 10 yr after diagnosis, but others, particularly those with an aggressive phenotype, only survive for 2–3 yr. Given the dramatic differences in treatment response, great efforts have been made to investigate the genetic and epigenetic heterogeneity and cell signaling defects involved in PCa progression [4]. Many advanced approaches, including target-region sequencing, array-based gene expression, copy number variation (CNV), and whole-genome sequencing of tumor samples, have been taken to portray the genomic landscape in PCa [5–7]. These works have reported several PCa-related genomic alterations, including the most common *TMPRSS2-ERG* fusion, copy number gains of 8q, copy number losses of 3p, 8p, 10q, 13q, and 17p, as well as complex chains of oncogenic structural DNA rearrangements (chromoplexy). However, the functional consequence of many alterations remains unknown.

Recent exome sequencing of prostate tumors revealed specific genetic alterations in coding regions, leading to the identification of frequent mutations in the genes such as *SPOP*, *FOXA1*, *TP53*, and *PTEN* [8–10], and other genomic alterations in *PIK3CA/B*, *ZBTB16/PLZF*, and *AR* [11]. More recently, The Cancer Genome Atlas (TCGA) described a comprehensive genomic analysis of 333 PCa patients [12], and the International Cancer Genome Consortium performed genomic profiling of 477 localized, nonindolent prostate tumors [13], mainly in the Caucasian population. Together, genome-wide alterations in PCa have been extensively studied in men from Western populations. In contrast, while the incidence rate of PCa has been rising dramatically in cities such as Hong Kong and Shanghai [3], the landscape of genome alterations in Asian PCa cohorts remains incompletely characterized, becoming a major hurdle for comprehensive understanding of the molecular etiology of this fatal disease.

Please cite this article in press as: Ren S, et al. Whole-genome and Transcriptome Sequencing of Prostate Cancer Identify New Genetic Alterations Driving Disease Progression. Eur Urol (2017), http://dx.doi.org/10.1016/j.eururo.2017.08.027

Download English Version:

https://daneshyari.com/en/article/8778517

Download Persian Version:

https://daneshyari.com/article/8778517

Daneshyari.com