



Review

Current progress and questions in germline genetics of prostate cancer

William B. Isaacs^{a,*}, Jianfeng Xu^b

^a *Brady Urological Institute, Johns Hopkins University, School of Medicine, Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD, USA*

^b *North Shore University Health System, Research Institute, Evanston, IL, USA*

Received 10 July 2018; accepted 7 September 2018

Available online 2 November 2018

KEYWORDS

Genetic susceptibility;
BRCA2;
Single-nucleotide polymorphisms;
Mutations;
Germline genetics;
Prostate cancer

Abstract Dramatic progress has been made in the area of germline genetics of prostate cancer (PCa) in the past decade. Both common and rare genetic variants with effects on risk ranging from barely detectable to outright practice-changing have been identified. For men with high risk PCa, the application of genetic testing for inherited pathogenic mutations is becoming standard of care. A major question exists about which additional populations of men to test, as men at all risk levels can potentially benefit by knowing their unique genetic profile of germline susceptibility variants. This article will provide a brief overview of some current issues in understanding inherited susceptibility for PCa.

© 2019 Editorial Office of Asian Journal of Urology. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

While over 1 111 700 men are diagnosed with prostate cancer (PCa) each year worldwide, fortunately a much smaller number (307 500) eventually die from this disease [1]. Understanding the role played by inherited factors in the progression of PCa to lethal disease has important translational impact on the detection, diagnosis and

prognosis of this common cancer. Specifically, being able to predict which men are more likely to develop a lethal PCa vs. an indolent one is currently an unmet clinical need.

Twin studies indicate that PCa is among the most heritable of all common cancers [2,3]. The past 10–12 years have seen dramatic progress in elucidating molecular factors affecting PCa susceptibility, with both common, single-nucleotide polymorphisms (SNPs) and rare genetic variants (high penetrance genes) playing fundamental roles.

2. Genetic risk score (GRS) and PCa

Since 2007, many PCa risk-associated SNPs have been identified through genome-wide association studies

* Corresponding author.

E-mail address: wisaacs@jhmi.edu (W.B. Isaacs).

Peer review under responsibility of Second Military Medical University.

(GWAS). To date, more than 163 SNPs have been consistently associated with risk of PCa [4]. SNPs are among the primary inherited determinants affecting gene expression and causal PCa risk SNPs, like those associated with other cancers, or other traits in general, are typically located in regulatory elements, e.g. gene promoters and enhancers, and can act as on-off or dimmer switches for individual gene expression levels and regulation.

Each SNP has a very modest individual effect on disease risk odds ratios (ORs: 1.05–1.20) but together they have a much stronger effect [5]. This cumulative effect can be measured using a GRS, a type of polygenic risk score, based upon one's genotype for a panel of risk associated SNPs [6]. GRS is weighted by the ORs of each SNP and is population-standardized, and making it accurate and easy to interpret. For example, GRS can be interpreted as a relative risk (RR) for the general population regardless of how many SNPs are used for the GRS calculation. A GRS of 1 indicates average risk. A GRS less than 1 and a GRS greater than 1 indicate lower risk and higher risk than the general population, respectively.

The clinical validity of GRS, i.e., the ability of GRS to accurately stratify risk, has been consistently established in many well-designed studies, including large case–control studies with samples sizes over 100 000 subjects [4,7], clinical trial populations [8–11], clinical prostate biopsy cohorts [12,13], and prospective studies [14]. In the largest genetic association study performed to date [4], GRS was significantly associated with PCa risk among 140 000 subjects. Compared to men in the 25th and 75th percentile of GRS, men in the 90th–99th percentile and top 1 percentile have RRs of 2.69 (95% confidence interval (CI): 2.55–2.82) and 5.71 (95% CI: 5.04–6.48), respectively.

There are several important clinical utilities of GRS. First, GRS can supplement family history information and the presence of mutations in high(er)-penetrance genes (HPGs) such as breast cancer susceptibility genes (*BRCA2*), ataxiatelangiectasia mutated (*ATM*), and homeobox b13 (*HOXB13*), to identify high-risk men for prostate-specific antigen (PSA) screening. In fact, more high-risk men in the general population can be identified through GRS than by family history and HPGs [11]. Second, GRS has a strong impact on PCa penetrance for HPG carriers. For example, in a large study of 933 male *BRCA2* carriers, the penetrance for PCa by age 85 was 40% among all the carriers but was 70% and 24% if their GRS was at top and bottom 5 percentile, respectively [15]. Third, GRS can also be used to supplement clinical variables such as PSA, PSA density, and digital rectal examination for decision making of prostate biopsy [8–13]. These results emphasized the compelling rationale for the translation of the use of GRS profiling to identify men most likely to benefit from PCa disease screening.

3. Genetic risk factors for lethal disease

As mentioned above, the most recent discoveries from Schumacher et al. [4] and Dadaev et al. [16] bring the number of common PCa risk SNPs to over 160, explaining an ~28% of familial relative risk for PCa. A major limitation of these markers, however, is that few if any of these

germline sequence variants can, individually or in combination, differentiate risk for an aggressive from indolent form of PCa [4,17]. Does this mean that inherited genetic variants specifically associated with aggressive PCa do not exist? To the contrary, study designs used in the past where a majority of patients studied have less aggressive disease undoubtedly presented a major barrier to discovery of genetic determinants of an aggressive PCa phenotype. In other words, quite simply, in order to find genetic risk factors for lethal PCa, one must study lethal PCa. Surprisingly, until recently, there have been very few large-scale sequencing studies of men with metastatic/lethal PCa.

Most previous studies searching for germline variants predisposing to more aggressive disease have been limited by the relatively small numbers of men with lethal or metastatic castrate resistant prostate cancer (mCRPC) that have been available for analysis. Indeed, most large study cohorts of PCa patients that have been available for study are derived from men undergoing surgical treatment for PCa (i.e., clinically localized disease), or are population-based, being composed of a representative distribution of patients in terms of tumor stage and grade. Since in the era of PSA screening most PCa diagnosed is well differentiated and clinically localized with very few lethal events, these cohorts are largely composed of cases that are understood to be de-enriched in men carrying significant germline risk factors for aggressive disease. This “dilution” factor has also been a major barrier to the success of studies using family history to enrich for genetic factors for PCa, since, again in the PSA era, many PCa families selected only on the basis of a PCa diagnosis, irrespective of disease stage or grade, are clusters of men with the form of PCa which is present at a very high frequency in the population, that is, small volume, organ confined, well differentiated disease. This form of PCa is highly likely to be indolent, and by virtue of its occurrence in the majority of aged men, highly unlikely to be driven by rare high penetrance cancer susceptibility genes.

A major reason for these suppositions comes from multiple recently reported sequencing studies of germline DNA of a particularly important segment of the PCa patient population, that is, men with mCRPC. Two landmark papers are of particular importance in this regard. Robinson et al. [18] identified mutations in three DNA repair genes, *BRCA1*, *BRCA2*, and *ATM*, at a surprisingly high rate in men unselected for age at diagnosis or family history, but rather for aggressive disease. Of 19 patients with biallelic inactivation of *BRCA2*, half had inherited a mutated inactive copy, a frequency 4 to 5 times higher than observed in previous studies of PCa patients. Subsequently, Pritchard et al. [19] demonstrated an elevated rate of germline mutations in a number of DNA repair genes in men with metastatic PCa. Importantly, the combined frequency of pathogenic mutations in a set of genes including *BRCA2* and *ATM* was higher than that reported in either the Exome Aggregation Consortium (ExAC) database of 53 000 unselected individuals or in the Cancer Genome Atlas (TCGA) database of men with clinically localized PCa.

Many previous studies had indicated that *BRCA2* was an important gene for PCa susceptibility. In 1997, Sigurdsson et al. [20] described the association of a deleterious founder mutation in *BRCA2* with aggressive PCa in Icelandic

families. Subsequently, multiple studies confirmed the link between PCa and *BRCA2* emphasizing *BRCA2* as a strong risk factor [21–23]. Castro et al. [25] and others have described and characterized *BRCA2* as an important prognostic factor for aggressive PCa [24–29]; however, the mutation frequency was low and most estimates suggested that *BRCA2* accounted for a very small fraction of PCa (1%–2%), even when early onset family history, positive cases were examined [30–32].

The studies by Robinson et al. [18], Pritchard et al. [19], and other similar studies, for the first time, provide strong evidence that inherited mutations may contribute to a substantial fraction of lethal PCa etiology and that such mutations can be exploited for differentiating risk for aggressive from indolent PCa [33]. Additional, critically important aspects of these findings are the therapeutic implications that arise as a result of PCa patients harboring drug-sensitizing mutations in DNA repair genes (e.g. the use of poly ADP-ribose polymerase [PARP] inhibitors to create a synthetic lethality in cancer cells deficient in homologous recombination repair due to deleterious mutations in *BRCA2* and other homologous recombination repair genes), as described by Mateo et al. [34], and the far reaching implications that inherited pathogenic mutations can have for family members [35].

While promising, largely due to mutation rarity, larger studies are urgently needed to better catalog germline pathogenic mutations in lethal PCa patients. More importantly, in-depth studies of large, well annotated patient populations are needed to establish associations between these mutations and lethal PCa, and to assess whether they can differentiate risk of lethal/aggressive PCa from indolent PCa.

4. Interaction of somatic and inherited genetic alterations to lethal/aggressive PCa

While somatic mutations play a required role in carcinogenesis, it is upon the fixed background of one's inherited genotype that these somatic mutations arise and contribute to the carcinogenic and tumor progression process. As such, the inherited genotype can have an impact on the spectrum of somatic alterations that lead to cancer development and behavior. To what extent genetic factors affect overall PCa aggressiveness is still debatable.

Epidemiological data provide support for heritability of aggressiveness of PCa. For example, PCa patients are found to be more likely to die of the disease if their father died of PCa [36]. Using a population-based database that includes ~3 million families to analyze the relationship of survival between sons and their fathers, Lindström et al. [36] found an increased hazard ratio of 2.07 (95% CI:1.13–3.79) for death from PCa in sons with poor father survival compared with those with good father survival, suggesting a genetic susceptibility for lethal PCa.

4.1. Somatic mutations

Intensive efforts have been devoted to identifying and characterizing somatic mutations in prostate tumors. Indeed, a wide array of DNA copy number alterations [37–48], fusion

genes [37,49–62], and point mutations [18,44,63–75] have been discovered. A recent study documented over 100 genes which were mutated at significant rates in PCa, marking the first time a comprehensive catalog of mutations in both localized and metastatic PCa is readily available [76]. Excitingly, somatic DNA alterations in *TP53*, *PTEN*, *CDK12*, *RB1*, *BRCA2*, *MYC* and *AR*, have clearly emerged as being among the most common and important drivers of metastatic/lethal vs. indolent disease.

4.2. Inherited mutations may influence susceptibility to somatic alterations via variations in DNA repair ability

Although somatic alterations may occur in cancer cells as a response to internal or external stress, the inherited genome can modulate the degree and types of these somatic alterations. A clear example of this is microsatellite instability resulting from mismatch repair defects in cancer cells which have mutations in mismatch repair genes including *MLH1*, *MSH2*, *MSH6*, and *PMS2*. Cancer cells with bi-allelic inactivation of these genes through either inherited or somatic loss of function (LOF) mutations, loss of heterozygosity (LOH) or both are characterized by hundreds to thousands of point mutations and small indels throughout the genome. Clinically, due to the high number of neoantigens generated by this hypermutation phenotype, patients with mismatch repair defects are prime candidates for checkpoint blockade and other evolving immunotherapies [77]. Intriguingly, genomic rearrangements associated with somatic *CDK12* mutations may elicit similar therapeutically relevant immunogenic neoantigens [78].

In PCa the genetic instability incurred when critical DNA repair genes and pathways are inactivated may drive tumor progression to a more lethal phenotype, possibly by direct mutational inactivation of genes suppressing invasion or other aspects of the metastatic process.

Similarly, the inability to repair double strand breaks by virtue of inactivating mutations in homologous recombination repair genes can generate specific genomic signatures of copy number changes, and other mutational events [79]. In this context, the survival and clonal expansion of cancer cells with increased genetic instability due to DNA repair defects reflects a balance between decreased fitness as a result of compromised ability to repair DNA and the selectable prosurvival, proliferation states afforded by inactivation of genes involved in apoptosis/tumor suppressor/checkpoint inhibition and deregulated growth promoting pathways.

5. Summary and conclusions

It is becoming apparent that stratification of men at all risk levels is possible using germline genetic markers: Men undiagnosed for PCa can benefit from knowing their risk of any PCa diagnosis as determined by common genetic variants, as well as their risk of aggressive/lethal disease, as conferred by rare pathogenic mutations in genes like *BRCA2* and *ATM*. Men diagnosed with low risk PCa can be informed of their suitability for treatment by active surveillance [80], and men diagnosed with high risk disease can benefit by

identification of optimal treatment regimens. Using a combination of common and rare genetic variants, a personalized program of disease screening before diagnosis, and disease management and treatment after diagnosis can be designed.

Some of the recent progress in the area of PCa genetics is summarized below:

- Loss of function mutations in DNA repair genes are present in ~5%–20% of lethal PCa cases. The repair genes most frequently sequenced are derived largely from the breast ovarian cancer (BRCA) panels used for genetic testing in breast and ovarian cancer. These panels typically include *BRCA1* and *BRCA2*, *ATM*, *BARD1*, *BLM*, *BRIP1*, *CHEK2*, *ERCC2*, *FANCG*enes, *MSH2*, *MSH6*, *NBN*, *PALB2*, *PMS2*, *PTEN*, *RAD51B*, and *RAD51B*, *TP53*, and *WRN*. These genes represent the major DNA repair pathways, with emphasis on homologous recombination and mismatch repair pathways. The variation of frequencies of mutations reported in different studies is the result of 1) different sets and different numbers of DNA repair genes being assayed, and 2) differing numbers of carriers of founder mutations, particularly in *BRCA2* (e.g. *S1982fs* Ashkenazi founder mutation) in different study populations. These founder mutations can substantially alter the mutation frequencies observed in different study populations.
- In virtually all published series of genetic testing in men with advanced PCa (CRPC) *BRCA2* is consistently observed to be the most frequently mutated gene, followed by *ATM* and *CHEK2*. Mutations in *BRCA2* and *ATM* are the only genes which are consistently observed to be more common in cases with lethal disease vs. indolent disease; possibly *CHEK2*, *PALB2* and *MSH2* also may distinguish risk for more aggressive disease but more data are needed.
- Somewhat surprisingly, the likelihood of inherited mutations in DNA repair genes in an individual is largely unrelated to family history of PCa [19]. A family history of other adenocarcinomas, particularly of the breast, pancreas, and/or colon, is just as predictive, if not more so, than a family history positive for PCa. This is likely not the case for individuals having multiple family members with advanced PCa, particularly at young age.
- A critical characteristic of common variants is their ability to affect the penetrance of *BRCA2* and most likely other high penetrance genes.
- Much more whole exome sequencing data are needed to identify novel genes associated with susceptibility and/or treatment sensitivity. So far, *HOXB13* is the only non-DNA repair genes discovered that is consistently associated with inherited risk for PCa [80].

6. Questions

When and who to screen with germline genetic testing? Should all men be tested?

What variants should be tested for?

Which genes are most prognostic? Are there genes other than *BRCA2* and *ATM* which are consistently associated with

high risk disease, and if so how can we find them? Currently only 15% or less of men with advanced disease harbor a pathogenic germline DNA repair gene mutation.

Do common variants affect the penetrance of all high penetrance genes?

What is the spectrum of high penetrance gene mutations in African Americans? Can these genes explain any of the high incidence and mortality rates from PCa in this understudied high risk population?

Author contributions

Study design: William B. Isaacs, Jianfeng Xu.

Drafting of the manuscript: William B. Isaacs, Jianfeng Xu.

Critical revision of the manuscript: William B. Isaacs.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgements

We acknowledge William T Gerrard, Mario Duhon, Jennifer and John Chalsty, Mr. Bob Aikens, Peter Bing, Warren Schwerin, and Frank Strang for their generous support of Dr. William Isaacs.

This article is dedicated to Donald S Coffey, Ph, who was mentor, teacher, colleague and dearest of friends for over 38 years. I remember many discussions with Dr. Coffey about the value of the genetic analyses my lab was pursuing in our quest to understand mechanisms of prostate carcinogenesis and progression. While he was wildly supportive, he would also emphatically caution that DNA sequence alone was far from the complete answer, and that one needed to consider a number of other realms, including epigenetics, complexity, self-organization, symmetry, structure, tensegrity, non-linear thermodynamics, punctuated evolution, phase shifts, alternate splicing, imprinting, chemomechanics, parallel computing network, entropy, collective behavior, information transfer, to name a few. Dr. Coffey always delighted in new ways of looking at biology and its complexities, never being satisfied with the status quo when it came to our understanding of normal life processes and the altered states that occur in disease. He was a world's expert in a wide spectrum of areas including the biochemistry of sulfhydryls, amine oxidases, DNA and nuclear structure, reproductive biology, enzyme kinetics and reaction mechanisms, steroid hormone metabolism, animal models of prostate pathology, predictive biomarkers, cell kinetics, cell movement, and unceasingly supporting and inspiring his trainees. Dr. Coffey was a psychedelic visionary of the highest order, always seeking to expand students' minds with novel concepts and bold idea-kindled creativity. Driving this process was a unique soul of gold, and a glowing heart infused with catalytic rhodium, always teaching, always supporting, always learning and growing. It was a true blessing and great honor to know him.

References

- [1] Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin* 2015; 65:87–108.
- [2] Lichtenstein P, Holm NV, Verkasalo PK, Iliadou A, Kaprio J, Koskenvuo M, et al. Environmental and heritable factors in the causation of cancer—analyses of cohorts of twins. *N Engl J Med* 2000;343:78–85.
- [3] Mucci LA, Hjelmborg JB, Harris JR, Czene K, Havelick DJ, Scheike T, et al. Familial risk and heritability of cancer among twins in Nordic countries. *J Am Med Assoc* 2016;315:68–76.
- [4] Schumacher FR, Al Olama AA, Berndt SI, Benlloch S, Ahmed M, Saunders EJ, et al. Association analyses of more than 140,000 men identify 63 new prostate cancer susceptibility loci. *Nat Genet* 2018;50:928–36.
- [5] Zheng SL, Sun J, Wiklund F, Smith S, Stattin P, Li G, et al. Cumulative association of five genetic variants with prostate cancer. *N Engl J Med* 2008;358:910–9.
- [6] Conran CA, Na R, Chen H, Jiang D, Lin X, Zheng SL, et al. Population-standardized genetic risk score: the SNP-based method of choice for inherited risk assessment of prostate cancer. *Asian J Androl* 2016;18:520–4.
- [7] Al Olama AA, Kote-Jarai Z, Berndt SI, Conti DV, Schumacher F, Han Y, et al. A meta-analysis of 87,040 individuals identifies 23 new susceptibility loci for prostate cancer. *Nat Genet* 2014; 46:1103–9.
- [8] Kader AK, Sun J, Reck BH, Newcombe PJ, Kin ST, Hsu FC, et al. Potential impact of adding genetic markers to clinical parameters in predicting prostate biopsy outcomes in men following an initial negative biopsy: findings from the REDUCE trial. *Eur Urol* 2012;62:953–61.
- [9] Chen H, Na R, Packiam VT, Conran CA, Jiang D, Tao S, et al. Reclassification of prostate cancer risk using sequentially identified SNPs: results from the REDUCE trial. *Prostate* 2017; 77:1179–86.
- [10] Sun J, Na R, Hsu FC, Zheng SL, Wiklund F, Condreay LD, et al. Genetic score is an objective and better measurement of inherited risk of prostate cancer than family history. *Eur Urol* 2013;63:585–7.
- [11] Chen H, Liu X, Brendler CB, Ankerst DP, Leach RJ, Goodman PJ, et al. Adding genetic risk score to family history identifies twice as many high-risk men for prostate cancer: results from the prostate cancer prevention trial. *Prostate* 2016;76:1120–9.
- [12] Jiang H, Liu F, Wang Z, Na R, Zhang L, Wu Y, et al. Prediction of prostate cancer from prostate biopsy in Chinese men using a genetic score derived from 24 prostate cancer risk-associated SNPs. *Prostate* 2013;73:1651–9.
- [13] Ren S, Xu J, Zhou T, Jiang H, Chen H, Liu F, et al. Plateau effect of prostate cancer risk-associated SNPs in discriminating prostate biopsy outcomes. *Prostate* 2013;73:1824–35.
- [14] Gronberg H, Adolfsson J, Aly M, Nordström T, Wiklund P, Brandberg Y, et al. Prostate cancer screening in men aged 50–69 years (STHLM3): a prospective population-based diagnostic study. *Lancet Oncol* 2015;16:1667–76.
- [15] Lecarpentier J, Silvestri V, Kuchenbaecker KB, Barrowdale D, Dennis J, McGuffog L, et al. Prediction of breast and prostate cancer risks in male *BRCA1* and *BRCA2* mutation carriers using polygenic risk scores. *J Clin Oncol* 2017;35:2240–50.
- [16] Dadaev T, Saunders EJ, Newcombe PJ, Anokian E, Leongamornlert DA, Brook MN, et al. Fine-mapping of prostate cancer susceptibility loci in a large meta-analysis identifies candidate causal variants. *Nat Commun* 2018;9:2256.
- [17] Helfand BT, Roehl KA, Cooper PR, McGuire BB, Fitzgerald LM, Cancel-Tassin G, et al. Associations of prostate cancer risk variants with disease aggressiveness: results of the NCI-SPORE Genetics Working Group analysis of 18,343 cases. *Hum Genet* 2015;134:439–50.
- [18] Robinson D, Van Allen EM, Wu YM, Schultz N, Lonigro RJ, Mosquera JM, et al. Integrative clinical genomics of advanced prostate cancer. *Cell* 2015;161:1215–28.
- [19] Pritchard CC, Mateo J, Walsh MF, De Sarkar N, Abida W, Beltran H, et al. Inherited DNA repair gene mutations in men with metastatic prostate cancer. *N Engl J Med* 2016;375: 443–53.
- [20] Sigurdsson S, Thorlacius S, Tomasson J, Tryggvadottir L, Benediktsdottir K, Eyfjörð JE, et al. *BRCA2* mutation in Icelandic prostate cancer patients. *J Mol Med (Berl)* 1997;75: 758–61.
- [21] Narod SA, Neuhausen S, Vichodez G, Armel S, Lynch HT, Ghadirian P, et al. Rapid progression of prostate cancer in men with a *BRCA2* mutation. *Br J Cancer* 2008;99:371–4.
- [22] Mitra A, Fisher C, Foster CS, Jameson C, Barbachanno Y, Bartlett J, et al. Prostate cancer in male *BRCA1* and *BRCA2* mutation carriers has a more aggressive phenotype. *Br J Cancer* 2008;98:502–7.
- [23] Edwards SM, Evans DGR, Hope Q, Norman AR, Barbachano Y, Bullock S, et al. Prostate cancer in *BRCA2* germline mutation carriers is associated with poorer prognosis. *Br J Cancer* 2010; 103:918–24.
- [24] Gallagher DJ, Gaudet MM, Pal P, Kirchhoff T, Balistreri L, Vora K, et al. Germline *BRCA* mutations denote a clinicopathologic subset of prostate cancer. *Clin Cancer Res* 2010;16: 2115–21.
- [25] Castro E, Goh C, Olmos D, Saunders E, Leongamornlert D, Tymrakiewicz M, et al. Germline *BRCA* mutations are associated with higher risk of nodal involvement, distant metastasis, and poor survival outcomes in prostate cancer. *J Clin Oncol* 2013;31:1748–57.
- [26] Castro E, Goh C, Leongamornlert D, Saunders E, Tymrakiewicz M, Dadaev T, et al. Effect of *BRCA* mutations on metastatic relapse and cause-specific survival after radical treatment for localised prostate cancer. *Eur Urol* 2015;68: 186–93.
- [27] Maier C, Herkommer K, Luedeke M, Rinckleb A, Schrader M, Vogel W. Subgroups of familial and aggressive prostate cancer with considerable frequencies of *BRCA2* mutations. *Prostate* 2014;74:1444–51.
- [28] Akbari MR, Wallis CJD, Toi A, Trachtenberg J, Sun P, Narod SA, et al. The impact of a *BRCA2* mutation on mortality from screen-detected prostate cancer. *Br J Cancer* 2014;111: 1238–40.
- [29] Kote-Jarai Z, Leongamornlert D, Saunders E, Tymrakiewicz M, Castro E, Mahmud N, et al. *BRCA2* is a moderate penetrance gene contributing to young-onset prostate cancer: implications for genetic testing in prostate cancer patients. *Br J Cancer* 2011;105:1230–4.
- [30] Edwards SM, Kote-Jarai Z, Meitz J, Hamoudi R, Hope Q, Osin P, et al. Two percent of men with early-onset prostate cancer harbor germline mutations in the *BRCA2* gene. *Am J Hum Genet* 2003;72:1–12.
- [31] Agalliu I, Kwon EM, Zadory D, McIntosh L, Thompson J, Stanford JL, et al. Germline mutations in the *BRCA2* gene and susceptibility to hereditary prostate cancer. *Clin Cancer Res* 2007;13:839–43.
- [32] Sinclair CS, Berry R, Schaid D, Thibodeau SN, Couch FJ. *BRCA1* and *BRCA2* have a limited role in familial prostate cancer. *Cancer Res* 2000;60:1371–5.
- [33] Na R, Zheng SL, Han M, Yu H, Jiang D, Shah S, et al. Germline mutations in *ATM* and *BRCA1/2* distinguish risk for lethal and indolent prostate cancer and are associated with early age at death. *Eur Urol* 2017;71:740–7.

- [34] Mateo J, Carreira S, Sandhu S, Miranda S, Mossop H, Perez-Lopez R, et al. DNA-repair defects and olaparib in metastatic prostate cancer. *N Engl J Med* 2015;373:1697–708.
- [35] Giri VN, Knudsen KE, Kelly WK, Abida W, Andriole GL, Bangma CH, et al. Role of genetic testing for inherited prostate cancer risk: Philadelphia Prostate Cancer Consensus Conference 2017. *J Clin Oncol* 2018;36:414–24.
- [36] Lindström LS, Hall P, Hartman M, Wiklund F, Grönberg H, Czene K. Familial concordance in cancer survival: a Swedish population-based study. *Lancet Oncol* 2007;8:1001–6.
- [37] Liu W, Chang B, Sauvageot J, Dimitrov L, Gielzak M, Li T, et al. Comprehensive assessment of DNA copy number alterations in human prostate cancers using Affymetrix 100K SNP mapping array. *Genes Chromosomes Cancer* 2006;45:1018–32.
- [38] Liu W, Chang BL, Cramer S, Koty PP, Li T, Sun J, et al. Deletion of a small consensus region at 6q15, including the *MAP3K7* gene, is significantly associated with high-grade prostate cancers. *Clinical Cancer Res* 2007;13:5028–33.
- [39] Lapointe J, Li C, Giacomini CP, Salari K, Huang S, Wang P, et al. Genomic profiling reveals alternative genetic pathways of prostate tumorigenesis. *Cancer Res* 2007;67:8504–10.
- [40] Liu W, Xie CC, Zhu Y, Li T, Sun J, Cheng Y, et al. Homozygous deletions and recurrent amplifications implicate new genes involved in prostate cancer. *Neoplasia* 2008;10:897–907.
- [41] Sun J, Liu W, Adams TS, Sun J, Li X, Turner AR, et al. DNA copy number alterations in prostate cancers: a combined analysis of published CGH studies. *Prostate* 2007;67:692–700.
- [42] Liu W, Laitinen S, Khan S, Vihinen M, Kowalski J, Yu G, et al. Copy number analysis indicates monoclonal origin of lethal metastatic prostate cancer. *Nat Med* 2009;15:559–65.
- [43] Castro P, Creighton CJ, Ozen M, Berel D, Mims MP, Ittmann M. Genomic profiling of prostate cancers from African American men. *Neoplasia* 2009;11:305–12.
- [44] Taylor BS, Schultz N, Hieronymus H, Gopalan A, Xiao Y, Carver BS, et al. Integrative genomic profiling of human prostate cancer. *Cancer Cell* 2010;18:11–22.
- [45] Beroukhi R, Mermel CH, Porter D, Wei G, Raychaudhuri S, Donovan J, et al. The landscape of somatic copy-number alteration across human cancers. *Nature* 2010;463:899–905.
- [46] Rose AE, Satagopan JM, Oddoux C, Zhou Q, Xu R, Olshen AB, et al. Copy number and gene expression differences between African American and Caucasian American prostate cancer. *J Trans Med* 2010;8:70.
- [47] Liu W, Lindberg J, Sui G, Luo J, Egevad L, Li T, et al. Identification of novel CHD1-associated collaborative alterations of genomic structure and functional assessment of CHD1 in prostate cancer. *Oncogene* 2012;31:3939–48.
- [48] Liu W, Xie CC, Thomas CY, Kim ST, Lindberg J, Egevad L, et al. Genetic markers associated with early cancer-specific mortality following prostatectomy. *Cancer* 2013;119:2405–12.
- [49] Tomlins SA, Rhodes DR, Perner S, Dhanasekaran SM, Mehra R, Sun XW, et al. Recurrent fusion of *TMPRSS2* and *ETS* transcription factor genes in prostate cancer. *Science* 2005;310:644–8.
- [50] Cerveira N, Ribeiro FR, Peixoto A, Costa V, Henrique R, Jerónimo C, et al. *TMPRSS2-ERG* gene fusion causing ERG overexpression precedes chromosome copy number changes in prostate carcinomas and paired HGPIN lesions. *Neoplasia* 2006;8:826–32.
- [51] Hermans KG, van Marion R, van Dekken H, Jenster G, van Weerden WM, Trapman J. *TMPRSS2:ERG* fusion by translocation or interstitial deletion is highly relevant in androgen-dependent prostate cancer, but is bypassed in late-stage androgen receptor-negative prostate cancer. *Cancer Res* 2006;66:10658–63.
- [52] Soller MJ, Isaksson M, Elfving P, Soller W, Lundgren R, Panaqopoulos I. Confirmation of the high frequency of the *TMPRSS2/ERG* fusion gene in prostate cancer. *Genes Chromosomes Cancer* 2006;45:717–9.
- [53] Tomlins SA, Laxman B, Dhanasekaran SM, Helgeson BE, Cao X, Morris DS, et al. Distinct classes of chromosomal rearrangements create oncogenic *ETS* gene fusions in prostate cancer. *Nature* 2007;448:595–9.
- [54] Liu W, Ewing CM, Chang BL, Li T, Sun J, Turner AR, et al. Multiple genomic alterations on 21q22 predict various *TMPRSS2/ERG* fusion transcripts in human prostate cancers. *Genes Chromosomes Cancer* 2007;46:972–80.
- [55] Clark J, Merson S, Jhavar S, Flohr P, Edwards S, Foster CS, et al. Diversity of *TMPRSS2-ERG* fusion transcripts in the human prostate. *Oncogene* 2007;26:2667–73.
- [56] Kumar-Sinha C, Tomlins SA, Chinnaiyan AM. Recurrent gene fusions in prostate cancer. *Nat Rev Cancer* 2008;8:497–511.
- [57] Helgeson BE, Tomlins SA, Shah N, Laxman B, Cao Q, Prensner JR, et al. Characterization of *TMPRSS2:ETV5* and *SLC45A3:ETV5* gene fusions in prostate cancer. *Cancer Res* 2008;68:73–80.
- [58] Maher CA, Kumar-Sinha C, Cao X, Kalyana-Sundaram S, Han B, Jing X, et al. Transcriptome sequencing to detect gene fusions in cancer. *Nature* 2009;458:97–101.
- [59] Mosquera JM, Perner S, Genega EM, Sanda M, Hofer MD, Mertz KD, et al. Characterization of *TMPRSS2-ERG* fusion high-grade prostatic intraepithelial neoplasia and potential clinical implications. *Clin Cancer Res* 2008;14:3380–5.
- [60] Lin C, Yang L, Tanasa B, Hutt K, Ju BG, Ohqi K, et al. Nuclear receptor-induced chromosomal proximity and DNA breaks underlie specific translocations in cancer. *Cell* 2009;139:1069–83.
- [61] Haffner MC, Aryee MJ, Toubaji A, Esopi DM, Albadine R, Gurel B, et al. Androgen-induced TOP2B-mediated double-strand breaks and prostate cancer gene rearrangements. *Nat Genet* 2010;42:668–75.
- [62] Rubin MA. ETS rearrangements in prostate cancer. *Asian J Androl* 2012;14:393–9.
- [63] Kan Z, Jaiswal BS, Stinson J, Janakiraman V, Bhatt D, Stern HM, et al. Diverse somatic mutation patterns and pathway alterations in human cancers. *Nature* 2010;466:869–73.
- [64] Berger MF, Lawrence MS, Demicheli F, Drier Y, Cibulskis K, Sivachenko AY, et al. The genomic complexity of primary human prostate cancer. *Nature* 2011;470:214–20.
- [65] Kumar A, White TA, MacKenzie AP, Clegg N, Lee C, Dumpit RF, et al. Exome sequencing identifies a spectrum of mutation frequencies in advanced and lethal prostate cancers. *Proc Natl Acad Sci U S A* 2011;108:17087–92.
- [66] Barbieri CE, Baca SC, Lawrence MS, Demicheli F, Blattner M, Theurillat JP, et al. Exome sequencing identifies recurrent *spop*, *foxa1* and *med12* mutations in prostate cancer. *Nat Genet* 2012;44:685–9.
- [67] 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.
- [68] Lindberg J, Mills IG, Klevebring D, Liu W, Neiman M, Xu J, et al. The mitochondrial and autosomal mutation landscapes of prostate cancer. *Eur Urol* 2013;63:702–8.
- [69] 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.
- [70] Weischenfeldt J, Simon R, Feuerbach L, Schlangen K, Weichenhan D, Minner S, et al. Integrative genomic analyses reveal an androgen-driven somatic alteration landscape in early-onset prostate cancer. *Cancer Cell* 2013;23:159–70.
- [71] Pritchard CC, Morrissey C, Kumar A, Zhang X, Smith C, Coleman I, et al. Complex *MSH2* and *MSH6* mutations in hypermutated microsatellite unstable advanced prostate cancer. *Nat Commun* 2014;5:4988.

- [72] Cooper CS, Eeles R, Wedge DC, Van Loo P, Gundem G, Alexandrov LB, et al. Analysis of the genetic phylogeny of multifocal prostate cancer identifies multiple independent clonal expansions in neoplastic and morphologically normal prostate tissue. *Nat Genet* 2015;47:367–72.
- [73] Gundem G, Van Loo P, Kremeyer B, Alexandrov LB, Tubio JMC, Papaemmanuil E, et al. The evolutionary history of lethal metastatic prostate cancer. *Nature* 2015;520:353–7.
- [74] Hong MK, Macintyre G, Wedge DC, Van Loo P, Patel K, Lunke S, et al. Tracking the origins and drivers of subclonal metastatic expansion in prostate cancer. *Nat Commun* 2015;6:6605.
- [75] Boutros PC, Fraser M, Harding NJ, de Borja R, Trudel D, Lalonde E, et al. Spatial genomic heterogeneity within localized, multifocal prostate cancer. *Nat Genet* 2015;47:736–45.
- [76] Armenia J, Wankowicz SAM, Liu D, Gao J, Kundra R, Reznik E, et al. The long tail of oncogenic drivers in prostate cancer. *Nat Genet* 2018;50:645–51.
- [77] Isaacsson Velho P, Antonarakis ES. PD-1/PD-L1 pathway inhibitors in advanced prostate cancer. *Expert Rev Clin Pharmacol* 2018;11:475–86.
- [78] Wu YM, Cieřlik M, Lonigro RJ, Vats P, Reimers MA, Cao X, et al. Inactivation of CDK12 delineates a distinct immunogenic class of advanced prostate cancer. *Cell* 2018;173:1770–82.
- [79] Castro E, Jugurnauth-Little S, Karlsson Q, Al-Shahrour F, Piñeiro-Yañez E, Van de Poll F, et al. High burden of copy number alterations and c-MYC amplification in prostate cancer from *BRCA2* germline mutation carriers. *Ann Oncol* 2015;26:2293–300.
- [80] Carter HB, Helfand B, Mamawala M, Wu Y, Landis P, Yu H, et al. Germline mutations in *ATM* and *BRCA1/2* are associated with grade reclassification in men on active surveillance for prostate cancer. *Eur Urol* 2018. <https://doi.org/10.1016/j.eururo.2018.09.021>.