



# Overview of research on fusion genes in prostate cancer

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**Abstract:** Fusion genes are known to drive and promote carcinogenesis and cancer progression. In recent years, the rapid development of biotechnologies has led to the discovery of a large number of fusion genes in prostate cancer specimens. To further investigate them, we summarized the fusion genes. We searched related articles in PubMed, CNKI (Chinese National Knowledge Infrastructure) and other databases, and the data of 92 literatures were summarized after preliminary screening. In this review, we summarized approximated 400 fusion genes since the first specific fusion *TMPRSS2-ERG* was discovered in prostate cancer in 2005. Some of these are prostate cancer specific, some are high-frequency in the prostate cancer of a certain ethnic group. This is a summary of scientific research in related fields and suggests that some fusion genes may become biomarkers or the targets for individualized therapies.

**Keywords:** Prostate cancer; fusion gene; biomarker

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## Introduction

Prostate cancer (PCa) was the second most common malignant tumor of men worldwide with 899,000 new cases each year, accounted for 14% of all cancers. And it was the sixth cause of cancer-related death in men, especially in developed countries (1,2). It had the highest incidence in Australia, Europe and Northern America, and was also high in the African descent, Southern America and the Caribbean regions. In Asia, however, PCa accounted for only 1–10% of male tumor cases (3). In recent years, the incidence of PCa in China had been rising dramatically year by year. In Beijing, Shanghai and Guangzhou, the incidence of PCa had surpassed that of male bladder cancer, ranking first among male genitourinary tumors (4).

PCa was a highly heterogeneous disease including multiple molecular and clinicopathological subtypes. Among them, molecular changes included an important form of genomic alteration—chromosomal rearrangement, which

often led to gene fusion. With the rapid development of science and technologies, such as next-generation sequencing (NGS), we had a deeper understanding that chromosome rearrangement could lead to the development of disease. Chromosome rearrangement could be divided into two forms. First, the promoter or enhancer of one gene was randomly connected to another proto-oncogene, triggering the activation of the oncogene. For example, immunoglobulin (*IG*) or T-cell receptor (*TCR*) gene promoter region was integrated into *MYC* proto-oncogene, resulting in B or T cell malignant tumor (5). In the other case, the two genes fused through translocation, such as the specific “Philadelphia chromosome” BCR-ABL in chronic myelogenous leukemia (CML) (6,7). At present, the Mitelman Database of Chromosome Aberrations and Gene Fusions in Cancer had included 10,004 gene fusions (8).

In this review, we summarized the fusion genes associated with PCa. As shown in *Table 1* and *Table S1*, we not only

**Table 1** The list of fusion genes in prostate cancer

Fusion gene	Year	Sample	Function	Validation by independent technology (Y or N)	Reference
<i>TMPRSS2-ERG</i>	2005	Early- and late-stage prostate cancer, LNCaP, DU145	An early event in prostate carcinogenesis	N	(9-15)
<i>TMPRSS2-ETV1</i>	2005	Prostate cancer	–	N	(9,13,15)
<i>TMPRSS2-ETV4</i>	2006	Prostate cancer	–	N	(13,15,16)
<i>U19-Eaf2</i>	2006	Downregulated in advanced prostate cancer	Its overexpression can markedly induce apoptosis in prostate cancer cells and suppresses xenograft tumor growth	N	(17,18)
<i>C15orf21-ETV1</i>	2007	Prostate cancer	–	N	(13,19-23)
<i>TMPRSS2-ETV5</i>	2008	Prostate cancer	–	N	(13,15,19)
<i>SLC45A3-ETV5</i>	2008	Prostate cancer	–	N	(13,19)
<i>HERV-K-ETV1</i>	2008	Prostate cancer	–	N	(11,13,19,23)
<i>HNRPA2B1-ETV1</i>	2008	Prostate cancer	–	N	(13,19,20,24)
<i>CANT1-ETV1/ETV4</i>	2008	Prostate cancer	–	N	(20,25)
<i>HERVK17-ETV1</i>	2008	Prostate cancer	–	N	(21,26)
<i>EST14-ETV1</i>	2008	Prostate cancer	–	N	(13,21,24,26,27)
<i>DDX5-ETV4</i>	2008	Prostate cancer	–	N	(15,20)
<i>FLJ37254-ETV1</i>	2008	Prostate cancer	–	Y	(20)
<i>SLC45A3-ERG</i>	2008	Prostate cancer	–	N	(20,28-30)
<i>SLC45A3-ETV1/ETV5</i>	2008	Prostate cancer	–	Y	(13)
<i>ACSL3-ETV1</i>	2008	Prostate cancer	–	N	(11,23)
<i>SYT-SSX</i>	2008	Prostatic synovial sarcoma	–	Y	(31)
<i>SLC45A3-ELK4</i>	2009	Prostate cancer, benign prostate tissue, metastatic prostate cancer, PC-3, LNCaP, Met-4, 22Rv1, VCaP, MDA-PCA-2B	Regulate cell growth in both androgen-dependent and independent prostate cancer cells	N	(10,12,15,32-36)
<i>FOXP1/DDX5-ETV1</i>	2009	Prostate cancer	–	Y	(24)
<i>ZNF577-ZNF649, ZNF649-ZNF577</i>	2009	Prostate cancer	–	N	(35,37,38)
<i>RC3H2-RGS3</i>	2009	VCaP-Met, VCaP	–	N	(12,35,39)
<i>STRN4-GPSN2</i>	2009	Metastatic prostate cancer	–	Y	(35)
<i>MIPOL1-DGKB</i>	2009	LNCaP	–	Y	(35)
<i>HJURP-EIF4E2, INPP4-HJURP</i>	2009	Prostate cancer	–	Y	(35)
<i>LMAN2-AP3S1</i>	2009	VCaP	–	N	(12,35,39,40)
<i>USP10-ZDHHC7</i>	2009	VCaP	–	N	(35,39)

**Table 1** (continued)

Table 1 (continued)

Fusion gene	Year	Sample	Function	Validation by independent technology (Y or N)	Reference
<i>EIF4E2-HJURP, HJURP-INPP4A</i>	2009	VCaP	–	Y	(35)
<i>NDRG1-ERG</i>	2010	Prostate cancer	Association with clinical parameters	N	(29,30)
<i>SLC45A3-BRAF, ESRP1-RAF1, RAF1-ESRP1</i>	2010	Advanced prostate cancer	–	N	(41-43)
<i>MSMB-NCOA4</i>	2011	Prostate cancer, normal prostatic tissue, highest in the T2 and N2 samples	–	N	(37,44,45)
<i>HDAC8-CITED1</i>	2011	Prostate cancer	–	Y	(37)
<i>AZGP1-GJC3</i>	2011	Prostate cancer	–	N	(11,37)
<i>ALG5-PIGU, PIGU-ALG5</i>	2011	<i>TMPRSS2-ERG</i> rearranged prostate cancer	–	N	(11,38,46)
<i>TNPO1-IKBKB</i>	2011	<i>TMPRSS2-ERG</i> gene fusion positive samples	–	N	(11,38)
<i>UBE2L3-KRAS</i>	2011	DU145, metastatic prostate cancer	<i>UBE2L3-KRAS</i> produces a fusion protein, specific knock-down of which, attenuates cell invasion and xenograft growth. Ectopic expression of the <i>UBE2L3-KRAS</i> fusion protein exhibits transforming activity in RWPE prostate epithelial cells <i>in vitro</i> and <i>in vivo</i>	N	(47,48)
<i>ADCK4-NUMBL</i>	2011	Prostate cancer	–	N	(11,37,49)
<i>C9orf163-SEC16A, SMG5-TMEM79, KLK4-KLK3</i>	2011	Prostate cancer	–	N	(10,50)
<i>DUS4L-BCAP29</i>	2011	Prostate cancer, normal prostatic tissue	Overexpression of <i>DUS4L-BCAP29</i> promotes cell growth and motility, even in non-cancer cells	N	(37,51)
<i>NCKAP5-MGAT5, SH3BGR-RIPK4, C11orf41-RAG1, FAM154A-IRAK3, CCNT1-PANK1</i>	2011	Prostate cancer	–	N	(44,52)
<i>EIF3K-ACTN4, ADCK4-NUMBL, EIF3K-ACTN4, DAC8-CITED1</i>	2011	Prostate cancer	–	N	(37,53)

Table 1 (continued)

Table 1 (continued)

Fusion gene	Year	Sample	Function	Validation by independent technology (Y or N)	Reference
<i>DHX35-ITCH, NFS1-PREX1</i>	2011	VCaP	–	Y	(39)
<i>GAS6-RASA3, ARFGEF2-SULF2, BCAS4-BCAS3, RPS6KB1-TMEM49</i>	2011	Prostate cancer	–	N	(37,39)
<i>KLK2-ETV1</i>	2011	Prostate cancer	–	N	(11,38)
<i>FKBP5-ERG, TMPRSS2-FKBP5-ERG</i>	2011	Prostate cancer	Conferring a growth advantage to neoplastic cells	N	(38)
<i>SLC45A3-FLI1</i>	2012	Prostate cancer	–	Y	(54)
<i>TTY15-USP9Y, USP9Y-TTY15</i>	2012	Prostate cancer, normal prostatic tissues, nonmalignant tissue from other organs	–	N	(11,34,55,56)
<i>FZD6-SDC2</i>	2012	Castrate-resistant neuroendocrine prostate cancer	–	N	(57,58)
<i>C15orf21-MYC</i>	2012	Prostate cancer	–	N	(57-59)
<i>JAZF1-JJAZ1</i>	2012	Prostate cancer	–	N	(33,53)
<i>SLC45A3-FGFR2</i>	2013	Prostate cancer	–	Y	(60)
<i>CCNH-C5orf30</i>	2014	Prostate cancer	–	N	(11,61)
<i>CCNH-C5orf50</i>	2014	Prostate cancer	Cell cycle progression	N	(61)
<i>TMEM135-CCDC67</i>	2014	Prostate cancer	–	N	(11,61)
<i>KDM4B-AC011523.2</i>	2014	Prostate cancer	Histone demethylation	N	(11,61)
<i>TRMT11-GRIK2</i>	2014	Recurrent prostate cancer after radical prostatectomy	RNA stability	N	(11,61,62)
<i>MTOR-TP53BP1</i>	2014	Recurrent prostate cancer after radical prostatectomy	Cell cycle progression	N	(11,61,62)
<i>LRRC59-FLJ60017</i>	2014	Recurrent prostate cancer after radical prostatectomy	Fibroblast growth factor nuclear import	N	(11,61)
<i>SLC45A2-AMACR</i>	2014	Prostate cancer	Fatty acid metabolism, associated with chemical recurrence	N	(11,61,62)
<i>MAN2A1-FER</i>	2014	PC3, DU145	Protein glycosylation, associated with prostate cancer recurrence	N	(11,61-63)
<i>DOT1L-HES6</i>	2014	Prostate cancer	Drive androgen independent growth in prostate cancer	N	(46,64)
<i>EIF2AK1-ATR, GLYR1-SLC9A8</i>	2014	Prostate cancer	–	Y	(65)

Table 1 (continued)

Table 1 (continued)

Fusion gene	Year	Sample	Function	Validation by independent technology (Y or N)	Reference
<i>MYB-NFIB</i>	2015	Prostatic basal cell carcinomas	–	Y	(66)
<i>TMPRSS2-SKIL</i> , <i>SLC45A3-SKIL</i> , <i>MIPEP-SKIL</i> , <i>ACPP-SKIL</i> , <i>HMGN2P46-SKIL</i>	2015	ETS-negative prostate cancer	Upregulate the TGF- $\beta$ pathway	N	(41,46)
<i>C14orf80-TMEM121</i>	2015	Prostate cancer samples, normal samples	–	N	(49,53)
<i>MFGE8-HAPLN3</i>	2015	Prostate cancer	<i>MFGE8-HAPLN3</i> had a correlation with Gleason score. silencing <i>D2HGDH-GAL3ST2</i> fusion resulted in dramatic reduction of cell proliferation rate and cell motility	N	(49,53)
<i>CLN6-CALML4</i> , <i>NUDT14-JAG2</i> , <i>PRIM1-NACA</i> , <i>SCNN1A-TNFRSF1A</i> , <i>MBD1-CCDC11</i>	2015	Prostate cancer	–	N	(49,53)
<i>PROM2-KCNIP3</i> , <i>BAIAP2L2-SLC16A8</i> , <i>D2HGDH-GAL3ST2</i>	2015	LNCaP, RWPE-1	–	N	(49,53)
<i>CTNNBIP1-CLSTN1</i> , <i>CTBS-GNG5</i>	2015	Prostate cancer	–	N	(49,51,53)
<i>SIDT2-TAGLN</i> , <i>DHRS1-RABGGTA</i>	2015	Prostate cancer	–	N	(53,67)
<i>HARS2-ZMAT2</i>	2015	Prostate cancer	–	N	(11,67)
<i>ZNF592-ALPK3</i> , <i>LMAN2-MXD3</i>	2015	RWPE-1	–	N	(49,53)
<i>SMG5-PAQR6</i>	2015	Prostate cancer	–	N	(10,53)
<i>MPP5-FAM71D</i>	2015	PC346C	Downregulation of <i>FAM71D</i> and <i>MPP5-FAM71D</i> transcripts in PC346C cells decreased proliferation	N	(68)
<i>ARHGEF3-C8ORF38</i>	2015	G089	–	N	(68)
<i>SND1-BRAF</i> , <i>EPB41L5-PCDP1</i> , <i>PHF20L1-LRRRC6</i>	2015	Prostate cancer	<i>SND1-BRAF</i> may contribute to the enhanced RAS/RAF/MAPK signaling observed with progression to castration-resistant prostate cancer	N	(69)

Table 1 (continued)

Table 1 (continued)

Fusion gene	Year	Sample	Function	Validation by independent technology (Y or N)	Reference
<i>CDC27-OAT</i>	2016	African American prostate cancer	–	Y	(70)
<i>TMED4-DDX56, AP5S1-MAVS</i>	2016	Prostate cancer	–	Y	(49)
<i>RLN1-RLN2, RLN2-RLN1</i>	2016	The normal and prostate cancer tissues, LNCaP	–	N	(71,72)
<i>NONO-TFE3</i>	2016	Prostate cancer	–	Y	(73)
<i>ACER3-B3GNT6</i>	2017	Overrepresentation in tumors and underrepresentation in benign tissues	Glycoprotein biosynthesis	N	(10)
<i>PXDN-AC144450.2</i>	2017	Overrepresentation in tumors and underrepresentation in benign tissues	A lincRNA gene	N	(10)
<i>RP11_17A19.1-KCTD1, RP11_321F6.1-SMAD6</i>	2017	Prostate cancer, normal prostatic tissues	LincRNAs	N	(10)
<i>ZNF841-ZNF432, ZNF551-ZNF776</i>	2017	Prostate cancer, normal prostatic tissues	Transcript regulation	N	(10)
<i>ACSS1-APMAP</i>	2017	Prostate cancer, normal prostatic tissues	–	N	(10)
<i>TMEM219-TAOK2</i>	2017	Prostate cancer	The apoptotic process	N	(10)
<i>NSUN4-FAAH</i>	2017	Prostate cancer	Fatty acid metabolism	N	(10)
<i>SSBP2-CPNE4</i>	2017	Prostate cancer	Membrane trafficking	N	(10)
<i>SPON2-CTBP1</i>	2017	Prostate cancer	Cell adhesion	N	(10)
<i>DNAJB1-TECR, GOLM1-NAA35</i>	2017	Prostate cancer	–	N	(10)
<i>DUSP11-C2orf11, DUSP11-C2orf78</i>	2017	Prostate cancer	–	Y	(74)
<i>KLK2-FGFR2</i>	2017	Prostate cancer	–	Y	(75)

ETS, erythroblast transformation specific; lincRNA, long intergenic non-coding RNA.

listed the fusion genes found in PCa in order by the year of discovery, but also summarized the types of specimens and the physiological effects and the carcinogenic mechanisms.

### TMPRSS2-ERG

Using the cancer outlier profile analysis (COPA) technique, Tomlins *et al.* found two new fusion genes in

PCa: *TMPRSS2-ERG* and *TMPRSS2-ETV1*, published in the journal “*Science*” in the Oct 28th, 2005 (9). As a transmembrane serine protease, *TMPRSS2* (transmembrane protease serine 2) is expressed in normal prostate cells and PCa cells. *TMPRSS2* is located at 21q22.3, composed of 14 exons and transcribed into a 3.8-kb transcript. *TMPRSS2* encodes a protein containing 492 amino acids. The promoter region of *TMPRSS2* has an androgen responsive elements (ARE), and its expression is induced

by androgen in androgen-sensitive PCa cells (76-78). This type II transmembrane proteinase contains four domains: serine protease domain, cysteine-rich scavenger receptor domain, low-density lipoprotein (LDL) receptor domain and transmembrane domain. *TMPRSS2* expression was significantly increased in PCa and benign prostatic hyperplasia (BPH) tissues, which was correlated with PCa Gleason score. And *TMPRSS2* ectopically expressed in highly malignant PCa, occurring in cytoplasm and cell membrane (79). Erythroblast transformation specific (ETS) transcription factor family includes ERG, ETV1, ETV4 and other members, which are located at 21q22.2, 7p21.2 and 17q21, respectively. These transcription factors play important roles in many physiological and pathological processes by regulating cell proliferation, differentiation, apoptosis and cell-cell interaction (9,16). ERG (v-ets erythroblastosis virus E26 oncogene homolog) is mainly expressed in mesodermal tissues and a few ectodermal tissues, such as urogenital cells and neural crest cells. ERG contains a highly conserved domain of 85 amino acids, which can bind to the DNA sequence 5'-GGA(A/T)-3' in the promoter (24). ERG overexpression might promote carcinogenesis by activating c-MYC, and disrupt normal differentiation of prostate epithelial cells (80). Transgenic mice were used to express truncated ERG products encoded by *TMPRSS2-ERG*. After 12–14 weeks, 3/8 (37.5%) mice developed into micro-prostate intraepithelial neoplasia (mPIN). These results suggested that ERG could induce prostate neoplasia in mice, supporting its carcinogenic role, but not enough to cause PCa progression (81). However, Kral *et al.* believed that the fusion of *TMPRSS2-ERG/EVTI/EVT4* could directly increase the chance of cell malignant change and eventually lead to cancerization (82). Therefore, *TMPRSS2-ERG* fusion gene was considered to be the driver of PCa.

In addition to the *ERG* and *ETV1* genes, other members of the ETS family were also identified as new 3' fusion partners. *TMPRSS2-ETV4* fusion gene was found in PCa with a lower incidence than *TMPRSS2-ERG/ETV1* (16). While *TMPRSS2-ETV5* was also found in PCa by Helgeson's team (19). Besides ERG, ETV1, ETV4 and ETV5, FLI1 was the fifth ETS transcription factor involved in the PCa fusion genes (54) (*Table 1*).

In 2008, Helgeson's team discovered a novel 5' fusion partner *SLC45A3* (solute carrier family 45 member 3), forming the fusion gene *SLC45A3-ETV5*, which was the second most common 5' fusion partner of ERG except *TMPRSS2* (19,28). In 2010, *NDRG1* (N-myc downstream

regulated gene 1) was also identified as a new 5' fusion partner. And the three fusion genes: *TMPRSS2-ERG*, *SLC45A3-ERG* and *NDRG1-ERG*, could lead to the overexpression of the truncated ERG protein (29,30). Subsequently, two new ETV4 fusion genes: *KLK2-ETV4* and *CANT1-ETV4*, were reported in PCa (20,25). Both *KLK2* (kallikrein related peptidase 2) and *CANT1* (calcium activated nucleotidase 1) are androgen-induced and prostate-specific genes (25). Then, two novel fusion genes: *OR51E2-ETV1* and *UBTF-ETV4*, were identified and confirmed by fluorescent *in situ* hybridization (FISH) and reverse transcription-polymerase chain reaction (RT-PCR) in PCa cases (21). Among them, *OR51E2* (olfactory receptor, family 51, subfamily E, member 2) encodes a G-protein-coupled receptor. While upstream binding transcription factor (*UBTF*) is a widely expressed gene, encoding an HMG-box DNA-binding protein involved in the recruitment of RNA polymerase I to ribosomal DNA promoter regions. In addition, *HERVK17* (21,26), *C15orf21* (19-22), *EST14* (21,24,26,27), *14q133-q21.1* (21), *FOXP1* (24), *FLJ37254* (20), *HERV-K\_22q11.23* (19), *HNRPA2B1* (19,20,24) and *DDX5* (20,24) were identified as 5' fusion partners of ETS family members (*Table 1*). In addition, it is well known that *TMPRSS2-ERG* is a high-frequency fusion gene specifically expressed in PCa and is a potential biomarker for the diagnosis and prognosis of PCa. We investigated 76 relevant articles to calculate the correlation of *TMPRSS2-ERG* and PCa patients' features in 2018 (83). The meta-analysis results showed that *TMPRSS2-ERG* had a highly predictive potential. *TMPRSS2-ERG* was associated with T-stage, metastasis and Gleason scores of PCa, but not with biochemical recurrence or specific mortality (83).

### **SLC45A3-ELK4**

*SLC45A3* (solute carrier family 45 member 3) is a prostate-specific androgen-regulated gene. ELK4 (ETS transcription factor) is a member of the ETS transcription factor family, promoting cell growth in LNCaP cells. ELK4 was highly expressed in a subgroup of PCa samples compared with benign prostate tissues (10,32). *SLC45A3-ELK4* fusion was not formed by RNA trans-splicing, but the product of the cis-splicing of adjacent genes (33). The level of the *SLC45A3-ELK4* transcript was associated with PCa progression, and was the highest in metastatic PCa samples (33). The *SLC45A3-ELK4* fusion could regulate cell growth by the exogenous expression of the fusion (33).



Moreover, similar to other long intergenic non-coding RNA (lincRNA) molecules, the fusion RNA was enriched in the nuclear fraction (33).

### MSMB-NCOA4

*MSMB-NCOA4* fusion had been found by Nacu *et al.* (37), and its expression level had been confirmed in PCa and normal prostate tissues (44,45). The *MSMB-NCOA4* fusion was transcribed at very low level in PCa, regulated by androgen (45). The MSMB (beta-microseminoprotein) is one of immunoglobulin superfamily, located at chromosome 10q11.2. MSMB is synthesized and secreted into seminal plasma by prostate epithelial cells. NCOA4 (nuclear receptor co-activator 4) locates adjacent to *MSMB* gene, and its expression product directly interacts with androgen receptor (AR) to promote AR transcriptional activity. Functional experiments showed that the *MSMB-NCOA4* fusion gene was related to the AR signaling pathway.

### MAN2A1-FER

The *MAN2A1-FER* fusion produced a chimera of 954 amino acids, including the N-terminal glycoside hydrolase domain and the mannosidase domain from *MAN2A1* and the tyrosine protein kinase domain from *FER* (11,61-63). Oncogene *FER* was a tyrosine kinase, and its overexpression was associated with the poor prognosis of several cancers. Many studies showed that *FER* activated AR and NF- $\kappa$ B signal pathways (84). In addition, the signal peptide of *MAN2A1* (mannosidase a class 2A member) might bring the *MAN2A1-FER* fusion product to the Golgi matrix, which might cause the abnormal phosphorylation of glycoproteins to alter multiple signaling pathways in Golgi (11).

### SLC45A2-AMACR

*SLC45A2-AMACR* fusion resulted in a chimera protein that contained transmembrane domains from *SLC45A2* and the intact racemase domain from *AMACR* (11,61,62). *SLC45A2* (solute carrier family 45 member 2) is a solute carrier involved in melanin metabolism. *AMACR* (alpha-methylacyl-CoA racemase) is a kind of racemase that participates in branch fatty acid metabolism. *AMACR* has a mitochondrial localization signal peptide in its N-terminus. While the *SLC45A2-AMACR* fusion product had a signal peptide from *SLC45A2*, which located the chimeric protein in membranes and cytoplasm. The ectopic expression of

racemase might affect fatty acid-related signaling, which could lead to a variety of cancers. It was noteworthy that *SLC45A2-AMACR* fusion was associated with PCa chemical recurrence, and tumors with this fusion gene had the most aggressive clinicopathological features (62).

### USP9Y-TTTY15, CTAGE5-KHDRBS3, SDK1-AMACR and RAD50-PDLIM4

In 2012, Ren *et al.* found *USP9Y-TTTY15* fusion (19/54=35.2%) in Chinese PCa patients by RT-PCR (55). In 2014, Ren *et al.* also detected the *USP9Y-TTTY15* fusion in 105 pairs of PCa and adjacent normal tissues. They found that the expression level of *USP9Y-TTTY15* fusion was not higher in PCa tissues than that in adjacent normal tissues, and was not associated with the characteristics of advanced PCa (34). In 2015, Zhu *et al.* calculate the *TTTY15-USP9Y* score using data from 226 urine sediment samples (56). It was found that the *TTTY15-USP9Y* score was significantly higher in men with positive biopsy results than in men with negative biopsy results ( $P<0.001$ ). And the *TTTY15-USP9Y* score significantly increased the diagnostic rate of PCa ( $P=0.001$ ) (56). The high-frequency of the *USP9Y-TTTY15* fusion suggested that it might be a physiologic event and plays an important role in the development of PCa in the Chinese populations (11,55).

*USP9Y* (ubiquitin specific peptidase 9 Y-linked) encodes an ubiquitin-specific protease involved in spermatogenesis related to male infertility, while *TTTY15* (testis-specific transcript, Y-linked 15) is a non-coding RNA (ncRNA) (11). Both *USP9Y* and *TTTY15* are located on the Y chromosome and are close to each other (34). Interestingly, the transcript of the *USP9Y-TTTY15* fusion had not open reading frames (ORF), indicating that this fusion did not encode a functional protein but a testis-specific ncRNA (34,55).

In addition, Ren *et al.* also found three additional gene fusions: *CTAGE5-KHDRBS3* (20/54=37.0%), *SDK1-AMACR* (13/54=24.1%), and *RAD50-PDLIM4* (15/54=27.8%), occurred frequently in Chinese PCa cases, suggesting that these gene fusions might play vital roles in PCa cases in China (55). More than that, Ren *et al.* also found two other fusion transcripts encoding ncRNA: *PHF17-SNHG8* and *DYRK1A-CMTM4* (55). Overall, these findings suggested the differences of the PCa gene fusions were existed in different ethnic populations, and supported the idea that genomic rearrangements might be influenced by environmental factors.



### CDC27-OAT

African-American men were twice as likely as men from other ancestries to develop and die of PCa. Lindquist *et al.* sequenced 24 PCa specimens from African-American men, and found that only 21% and 8% of the African-American patients had *TMPRSS2-ERG* fusions and *PTEN* losses, far lower than those of European ancestry (70). They also identified the specific or more common mutations in African-American patients, such as the new fusion gene: *CDC27* (cell division cycle 27)-*OAT* (ornithine aminotransferase), occurring in 17% of patients (70). This meant that African-American men with more aggressive phenotype PCa were different from other races at the genomic level, which reinforced the significance of molecular changes in PCa progression.

### TMPRSS2-FKBP5-ERG

In addition to the more common fusion genes mentioned above, the researchers also found a rare and complex fusion gene *TMPRSS2-FKBP5-ERG* in PCa. This complex fusion involved the translocation and fusion of three genes, and its expression product promoted the growth of neoplastic cells (38).

### Non-coding fusion gene

PCa-related fusion genes could be divided into several categories according to function. The first category was kinase fusion genes, including: *RET*, *NTRK1*, *NTRK3*, *ALK*, *ROS1*, *FGFR1/2/3*, *CRAF*, *MAST1/2*, *RAF* family and serine/threonine kinase, etc. They had therapeutic importance, considered as the targets for treatment. The second classification was transcription factors: *ETS*, *NUT/UTM1*, *POU5F1*, *MAML2*, *NFIB*, *PLAG1*, *TFE3*, *NOTCH*, and *PAX8*, causing abnormal expression of downstream target genes in a variety of cancers. The third classification was signaling pathway protein: *Wnt/catenin* pathway, *TGF- $\beta$*  pathway, etc. Other categories included growth factor receptors (*GABBR2*, *ITPR2* and *TACSTD2*), co-factors (*GAB2* and *WIF1*), chromatin modifier genes (histone demethylase and histone methyltransferase), cytoskeletal proteins (*MYO19*, *SEC22B*, *SNF8*, *STXBP4*, *HIP1R* and *TPR*), and metabolic enzymes, etc. Furthermore, there were also some fusions that could lead to loss of function of genes, most of which involved tumor suppressor genes, such as *TP53* and *PTEN* (41).

We had mentioned three non-coding fusion genes in the above: *USP9Y-TTTY15*, *PHF17-SNHG8* and *DYRK1A-CMTM4*. In 2015, Luo *et al.* found two *MALAT1* fusions: *MALAT1-WDR74* and *MALAT1-TTN*, from a 21-year-old man prostate. *MALAT1* (metastasis associated lung adenocarcinoma transcript 1) is a long ncRNA, involved in RNA recombination and located at the active transcription regions. *MALAT1* had the oncogenic activity, and its overexpression was associated with the poor prognosis of several malignant tumors (11). The occurrence of *MALAT1-WDR74* fusion eliminated the translation initiation codon-ATG. Therefore, the fusion gene did not have any protein products (11). In addition, Zhao *et al.* also found that two fusion genes: *RP11\_17A19.1-KCTD1* and *RP11\_321F6.1-SMAD6*, which were predicted to encode lincRNAs, not proteins (10).

### Discussion

Throughout history, advances in science and technologies tend to bring new discoveries. As the advent of NGS techniques, the discovery of a large number of fusion genes is spawned. For the discovery of fusion genes, it is conceivable that transcriptome sequencing is more effective than genome sequencing. However, each high-throughput sequencing generates a large amount of data to be analyzed, so we need to develop the reliable and efficient computational methods for detecting gene fusions from RNA-seq data. Nowadays, several tools had been developed to detect large-scale chromosomal rearrangements. These tools included deFuse (10,85), InFusion (12), FusionMap (67), FusionSeq (41,86), FusionCatcher (87), SOAPfuse (34,88), TopHat-Fusion (39), ChimeraScan (89) and SlideSort-BPR (breakpoint reads) (90,91).

One of the foundations of these tools was to find the breakpoints of the cancer genome by mapping to the reference genome. One major drawback of this method was that the variation of the reference genome was so huge. Fusionseq (38,86) was the first computational tool to reveal fusion genes using RNA-seq data. This method was based on the recognition of discordantly read pairs, which was used to construct the connection libraries for possible exon fusion. Then, the reads would be re-adjusted to the construction library to find its fused connection point. If there was not a reference genome, we could detect breakpoints by comparing two assembled genomes. TopHat-Fusion (39) was an effective tool to discover

fusion genes without the existing annotations. Because it was independent of the gene annotations, TopHat-Fusion could find known fusion products, unknown genes, and unannotated splicing variants (39). In addition, SlideSort-BPR (breakpoint reads) (90,91) detected breakpoints by directly comparing data from two different type cells, without mapping them to the reference genomes or without the assembling reads. SlideSort-BPR identified the reads associated with the breakpoints by looking for “unbalanced” reads between the two sets of samples (90).

In conclusion, with the rapid development of science and technology, especially the high-throughput second-generation sequencing technology and bioinformatics algorithm, the discovery of fusion genes has ushered in an era of rapid development. Furthermore, to identify fusion genes that have the potential to drive carcinogenesis, scientists need to conduct in-depth studies on the role of fusion genes in cancer. On the one hand, it is necessary to confirm that the fusion genes are specifically expressed in PCa; on the other hand, it is necessary to look for the correlation between these fusion genes and the occurrence and development of PCa. Moreover, it is necessary to explore the molecular mechanism of their promotion of the progression of PCa. The content of this paper was the first step of these in-depth studies, summarizing the fusion genes that have been found to be expressed in PCa.

## Conclusions

To sum up, the formation of fusion genes is one of the important mechanisms to promote the development of PCa. Today, the advance of high-throughput sequencing has led to the discovery of many fusion genes. However, the discovery of PCa-specific fusion genes is lagging far behind the discovery of chromosomal abnormalities. Moreover, many fusion genes exist not only in cancer tissues, but also in benign tissues. In this review, we summarize the fusion genes found in PCa, some of which are PCa-specific fusion genes, and some are the fusion genes of high-frequency in the certain ethnic PCa. These specific fusion genes have great clinical value, not only to diagnose PCa as biomarkers, but also to inhibit the progression of PCa as the targets of biological agents.

## Clinical significance

The paper summarized more than 400 fusion genes that had been found in PCa. Some of these were expressed

specifically in PCa, and most of them indicated the subtype or the stage of PCa. The discovery of these specific fusion genes which could be used as biomarkers or drug targets, was greatly conducive to the clinical diagnosis and personalized treatment of PCa.

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## Footnote

*Conflicts of Interest:* Both authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr.2020.01.34>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Table S1 Other fusion genes in prostate cancer

Fusion gene	Year	Sample	Reference
<i>PMF1-BGLAP, BPTF-KPNA2, RBM14-RBM4, C15orf38-AP3S2, PLEKHO2-ANKDD1A, KIAA1984-C9orf86, GCSH-C16orf46, VMAC-CAPS, ENTPD5-FAM161B, TMC5-CP110, TPD52-MRPS28, IVD-BAHD1, KLK11-KLK7, IRS2-NUFIP1, ZNF763-CHST7, VAMP8-VAMP5, SEC31A-C6orf62, HHLA1-OC1R3, R3HDM2-NFE2, IQCJ-SCHIP1, KRT24-NCOR1, LIN37-GPSN2, NUP214-XKR3, C16orf58-NUPR1, MBPTS1-SERF2, GCN1L1-MSI1, LITAF-DECR2, TGOLN2-USP39, REV1-CPSF3, CAMTA1-SPPL3, DYNC1H1-EIF4B, MBPTS1-SERF2, OGT-RBM22, ROR2-USP36, TIMM9-PRKDC, ZDHHC8-UBL5</i>	2011	Prostate cancer	(37)
<i>H2AFJ-HBA2, NEAT1-ANO7, PTMS-TAF15, NEAT1-PCBD2, ENOSF1-KLK3, BCL2L2-SEPW1, MKL2-AMACR, ANO7-GOLM1, FKBP5-TMPRSS2, SP3-TFAP2A, ZBTB16-KLK3, ZBTB37-GABRB3, CDKN1A-CD9, SOCS4-ERG, DTX2-PMS2L5, MIER2-RSRC2, LRRFIP2-UBE2D3, TAGLN-SPSB3, FTH1-EIF5A, EEF1D-HDAC5, ENO1-APCDD1, PTPRN2-SLC25A10, PICK1-SLC16A8, WT-CD9, RYBP-FOXP1, MIER-RSRC2</i>	2011	Prostate cancer	(38)
<i>ZDHHC7-ABCB9, HJURP-EIF4E2, VWA2-PRKCH, RGS3-PRKAR1B, SPOCK1-TBC1D9B, LRP4-FBXL20, INPP4A-HJURP, C16orf70-C16orf48, NDUFV2-ENSG00000188699, NEAT1-ENSG00000229344, ENSG00000011405-TEAD1, WDR45L-ENSG00000249026, IMMT1-IMMT, ENSG00000214009-PCNA, CTNNA1-ENSG00000249026, LMAN2-AP3S1</i>	2011	Prostate cancer	(39)
<i>CTAGE5-KHDRBS3, SDK1-AMACR, RAD50-PDLIM4, PHF17-SNHG8, DYRK1A-CMTM4</i>	2012	Chinese prostate cancer	(55)
<i>TMEM55A-LCLAT1, ABL1-ANXA4, RALGPS1-EXOC6B, DENND1A-ANXA4, ZNF638-KCNS3-PPM1G, GPR107-C2orf28, SLC35D2-LPPR-MRPL50, LOC199899-JAK1, PRIM1-USP9X, USP9X-PRIM1, DNAJC11-NOTCH2, C14orf145-MOBP, UGDH-SLC25A31, DENND4A-RAB11A, RAB11A-DENND4A, ZNF410-PTGR2, SKIV2L2-SV2C, SESN1-MGST2, MLL5-DRAM1</i>	2012	Castrate-resistant neuroendocrine prostate cancer	(57)
<i>OR51E2-ETV1, 14q133-q21.1-ETV1, SLC45A3/HERVK17/UBTF-ETV4</i>	2013	Prostate cancer	(21)
<i>NDUFAF2-MAST4, PDE4D-FAM172A, PDE4D-PPP2R2B, ADAMTS12-PXDNL, PPP2R2B-FAM172A, PDE4D-C5orf47, CPLX2-UBXD8, EBF1-FBXL17, KCNN2-EBF1, RASGRF2-RNF145, JMY-DMGDH, TRIM40-FBXO38, EFNA5-PCDHB7, YTHDC2-PPP2R2B, PDE8B-UIMC1, ZFP62-RGNEF, EBF1-FEM1C</i>	2013	VCaP	(40)
<i>C12orf76-ANKRD13A, TMEM165-CLOCK, ACTR8-IL17RB, MTG1-LOC619207, KRTCAP3-IFT172, TMEM79-SMG5, NARG1-NDUFC1, SLC44A4-EHMT2, NCAPD3-JAM3, SLC16A8-BAIAP2L2, ZNF606-C19orf18</i>	2014	Prostate cancer	(90)
<i>ACSL3-ETV1, FLJ35294-ETV1, FOXP1-ETV1, C15orf21-ETV1, KLK2-ETV4, CANT1-ETV4, KDM4B-AC011523.1</i>	2015	Prostate cancer	(11)
<i>KLK4-KLKP1, PRKAA1-TTC33, C6orf47-BAG6, MALAT1-WDR74, MALAT1-TTN</i>	2015	Normal prostatic tissue	(11)
<i>TBXL1-PIK3CA, ACPP-PIK3CB, GRHL2-RSPO2</i>	2015	Prostate cancer	(41)
<i>NOS1AP-C1orf226, HARS-ZMAT2, CIQTNF3-AMACR</i>	2015	Prostate cancer	(67)
<i>MIPOL1-ETS, HNRPA2B1-ETV1, MIPOL1-SKIL</i>	2015	Prostate cancer	(46)
<i>ANKRD27-ALDH7A1, ZNF480-ALDH7A1, ELAVL1-ALDH7A1, NR3C1-HOXA9, SLC16A12-TESC, FAM154A-LRP1, IMMP2L-LYST, ENOX1-ANO2, WWOX-ENOX1, C1orf151-HLCS, HLCS-TTC3, HLCS-ERG, TTC3-CCDC21, TTC3-ERG, ENSG00000253819-PCNXL2, DISC1-PCNXL2, C11orf41-OR51E2, MLLT4-KIF25, GPHN-RGS6, GPHN-DPF3, VCL-ZNF503, RGS6-DPF3, ZNF578-EPN1, ANKRD27-ZNF578, KDM4B-ZNF578, LRP12-ENSG00000253350, ENSG00000254303-WDR67, PACRG-LOC285796, IPCEF1-PACRG</i>	2015	Prostate cancer	(52)
<i>INTRACHR-SS-0GAP, CHCHD10-VPREB3F, DTD2-HEATR5A, VAMP1-CD27-AS1, CLN6-CALML4, TMED4-DDX56, NUDT14-JAG2, PRIM1-NACA, ZNF592-ALPK3, LMAN2-MXD3, BAIAP2L2-SLC16A8, SLC39A1-CRTC2, METTL10-FAM53B, TFDP1-GRK1, KIAA0753-PITPNM3, CIRBP-C19orf24, TP53RK-SLC13A3, LINC00680-GUSBP4, PPP1R16A-GPT, ADSL-SGSM3, AKAP8L-AKAP8, AP5S1-MAVS, DMC1-DDX17, DMKN-KRTDAP, DPM2-PIP5K1L, MED12-NLGN3, RRM2-C2orf48, SLC29A1-HSP90AB1, TRADD-B3GNT9, WRB-SH3BGR, BRCA1-VAT1, DTD2-HEATR5A, RNF4-FAM193</i>	2015	Prostate cancer	(53)
<i>BLVRB-SERTAD3, FAM179B-PRPF39, DDX5-POLG2, GPR108-C3</i>	2015	LNCaP	(53)
<i>MPP5-FAM71D, ARHGEF3-C8ORF38</i>	2015	Prostate cancer	(68)
<i>SND1-BRAF, EPB41L5-PCDP1, PHF20L1-LRRC6</i>	2015		(69)
<i>Intergenic-NBEA, AAK1-AC114772.1, CTA-221G9.11-KIAA1671, POLR1D-LNX2, RP11-180P8.1-TANC2</i>	2016	LNCaP, VCaP	(12)
<i>SREBF2-XRCC6, FAM117B-BMPR2, GPS2-MPP2, RP11-534G20.3-SVIL, MIPOL1-DGKB, RERE-PIK3CD, Intergenic-AMZ2, CASZ1-KAZN</i>	2016	LNCaP	(12)
<i>SREBF2-XRCC6, FAM117B-BMPR2, GPS2-MPP2, RP11-534G20.3-SVIL, MIPOL1-DGKB, RERE-PIK3CD, Intergenic-AMZ2, CASZ1-KAZN</i>	2016	LNCaP	(12)
<i>VWA2-PRKCH, INSL6-JAK2, ZDHHC7-H3F3B, ZDHHC7-UNK1, HJURP-EIF4E2, PPIP5K2-CTC-340A15.2, ZDHHC7-UNK12, ZNF577-ZNF841, SPOCK1-Intergenic, HSF1-RERE, Intergenic-SH3D19, TIA1-DIRC2, CNNM4-PARD3B, AC024940.1-FAM60A, DIRC2-Intergenic</i>	2016	VCaP	(12)
<i>TMEM79-SGM5, SOD2-B3GNT6, SSBP2-SPNE4, DSCC1-KB_1471A8.1, FAM83H-RP11_429J17.6</i>	2017	Prostate cancer	(10)