TMPRSS2-ERG gene fusion in prostate cancer

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Background. The *TMPRSS2-ERG* gene fusion is one of the most widely spread chromosomal rearrangements in carcinomas. Since its discovery, a number of studies have examined its diagnostic, prognostic and therapeutic implications for prostate cancer where suitable biomarkers are still lacking. The publication data are inconsistent. The aim of this review was to critically evaluate the current clinical impact of this gene fusion.
Methods. The PubMed online database was used to search relevant reviews and original articles.
Results. Although the *TMPRSS2-ERG* gene fusion appears to be a suitable diagnostic biomarker, the prognostic implications of this gene fusion are still unclear. Several new strategies for therapeutically targeting ETS fusions and their modulators have been identified and are currently being investigated.
Conclusion. Due to the heterogeneity of prostate cancer, the combination of several biomarkers is necessary to accurately assess the presence of prostate cancer, predict its potential clinical outcome and decide on appropriate therapy (e.g. PARP inhibitors).

Key words: *TMPRSS2-ERG*, gene fusion, diagnosis, prognosis, predictive marker, prostate cancer

Received: September 18, 2014; Accepted with revision: November 25, 2014; Available online: December 5, 2014
http://dx.doi.org/10.5507/bp.2014.065

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INTRODUCTION

Prostate cancer (PCa) is the third most common cancer diagnosed in Europe today, and the most frequent cancer in European men[1]. It is a heterogenous disease displaying either an indolent or an aggressive course[2]. One of the major problems with its diagnosis and prognosis, is the lack of valid biomarkers. Elevated levels of serum prostate-specific antigen (PSA) and/or abnormal digital rectal examination (DRE) which form the rationale for histopathological examination by needle biopsy, are insufficient and can lead to overdiagnosis and overtreatment. It is also impossible to distinguish between indolent and aggressive forms of PCa (ref.[3]). The main focus of current PCa research is hence on identifying and validating new biomarkers[4]. This review covers recent knowledge on the importance of the *TMPRSS2-ERG* gene fusion in PCa.

GENES FUSIONS AND THEIR SIGNIFICANCE

Gene fusions resulting from chromosomal rearrangements are known to play an important role in the initial steps of tumorigenesis[5]. Tomlins et al.[6] first described a gene fusion between *TMPRSS2* (Transmembrane Protease Serine 2) gene and *ETS* (Erythroblastosis Virus E26 Transformation-Specific) family genes in PCa, involving the 5´- untranslated region of *TMPRSS2* (21q22) and the encoding region of some transcription factors such as the *ETS*-related gene (*ERG*, 21q22) or *ETS* variant 1 gene (*ETV1* 7p21). Bioinformatic analysis of DNA microarray data, subsequent fluorescence in situ hybridization (FISH) and reverse transcription polymerase chain reaction (RT-PCR) analysis, have identified *TPRSS2-ERG* fusion and *TMPRSS2-ETV1* fusion in 16/29 (55%) and in 7/29 (27%) cases of PCa, respectively[7]. Until this time, carcinomas were believed to harbor only rare disease-specific gene rearrangements, unlike leukemias, lymphomas and sarcomas[8].

TMPRSS2 is a prostate-specific, androgen regulated gene, constitutively expressed under the transcriptional control of androgens through androgen responsive elements (ARE) in its 5´UTR. The ETS family of transcription factors is one of the largest families of transcription regulators. All 27 members share a conserved DNA binding domain – the ETS-domain which permits binding to purine rich DNA sequences containing a 5´-GGAA/T-3´ core sequence[9]. ETS transcription factors play an important role in diverse biological processes, including cell proliferation, apoptosis, differentiation, angiogenesis and invasiveness. *TMPRSS2-ETS* gene fusions lead to increased expression of the ETS members in response to the androgen induced *TMPRSS2* promotor[10].

Further experiments revealed that the *TMPRSS2* gene could also be fused to other members of the ETS transcription factor family, such as *ETV4* and *ETV5* genes[11,12]. *ETV1*, *ETV4* and *ETV5* fusions together account for approximately 5-10% of PSA-screened PCa (ref.[13-15]). Likewise, other genes, for example, *SLC45A3* (Solute Carrier Family 45, Member 3), *NDRG1* (N-Myc Downstream Regulated 1), *HERPUD1* (Homocysteine-Inducible, Endoplasmatic Reticulum Stress-Inducible,

Ubiquitin-Like Domain Member 1) may fuse with the 3´region of ETS family members[12,13,16-18]. However, the *TMPRSS2-ERG* gene fusion accounts for most recurrent gene fusions in PCa (ref.[19]), with a frequency of 40-70%, which provides an idea of its potential as a biomarker[4,20].

On the base of the above, PCa can be divided into two distinct molecular subtypes, ETS fusion-positive and ETS fusion-negative, characterized by a different biological behavior and response to therapy[4,21-23].

INCIDENCE OF PROSTATE CANCER AND TMPRSS2-ERG

The incidence of PCa shows geographical and ethnic differences. The Asian population has a lower incidence of PCa than Caucasians, a difference purported to entail gene and lifestyle differences. The ETS gene fusion rate is highest in the United States (42-60%) and lowest in Asia (21% in Korea and 28% in Japan) (ref.[24,25]). Mosquera et al.[26] examined 100 prostate biopsy specimens from United States patients and reported that non-Caucasian patients were less likely to have a positive *TMPRSS2-ERG* fusion status than Caucasion patients. These genetic differences may underlie the regional/ethnic differences in clinical incidence and might be induced by specific environmental and/or genetic risk factors[27].

The *TMPRSS2-ERG* gene fusion is an early event in carcinogenesis and absent in benign prostatic hyperplasia (BPH) and proliferative inflammatory atrophy (PIA). The gene fusion is found in approximately 20% of high-grade prostatic intraepithelial neoplasia (HGPIN) lesions, and in around 50 % of localised cancers[6,28-32].

MECHANISM OF FUSION FORMATION

The relatively high frequency of the *TMPRSS2-ERG* gene fusion in PCa is the result of co-localization of both genes (*TMPRSS2*, *ERG*) on chromosome 21q22.2. The fusion of both genes is most often generated by an interstitial deletion where a region of approximately 2.8 Mb in the 21q22 locus is lost (known as Edel class), and to a lesser extent through an insertion of intervening region into another chromosome (known as Esplit class) (ref.[4,33-35]). The mechanism of fusion formation is summarized in Fig 1. The deletion of intervening region is observed in 39-60% of *TMPRSS2-ERG*–positive cases[36,37]. Roughly, 13 genes located in the area of the common deletion site are down-regulated. In addition to the oncogenic potential of the *TMPRSS2-ERG* fusion product, loss of at least two of these genes, *ETS2 (*V-Ets Avian Erythroblastosis Virus E26 Oncogene Homolog 2) and *HMGN1* (High Mobility Group Nucleosome Binding Domain 1) may be associated with cancer progression[36,38].

Mani et al.[39] demonstrated that androgen signalling induces chromosomal proximity between *TMPRSS2* and *ERG* loci, and facilitates the formation of the *TMPRSS2-ERG* gene fusion when subjected to enzyme TOP2B [Topoisomerase (DNA) II Beta 180kDa], that causes DNA double-strand breaks (DSBs). This enzyme catalyzes transient DSBs to resolve DNA topological constraints.

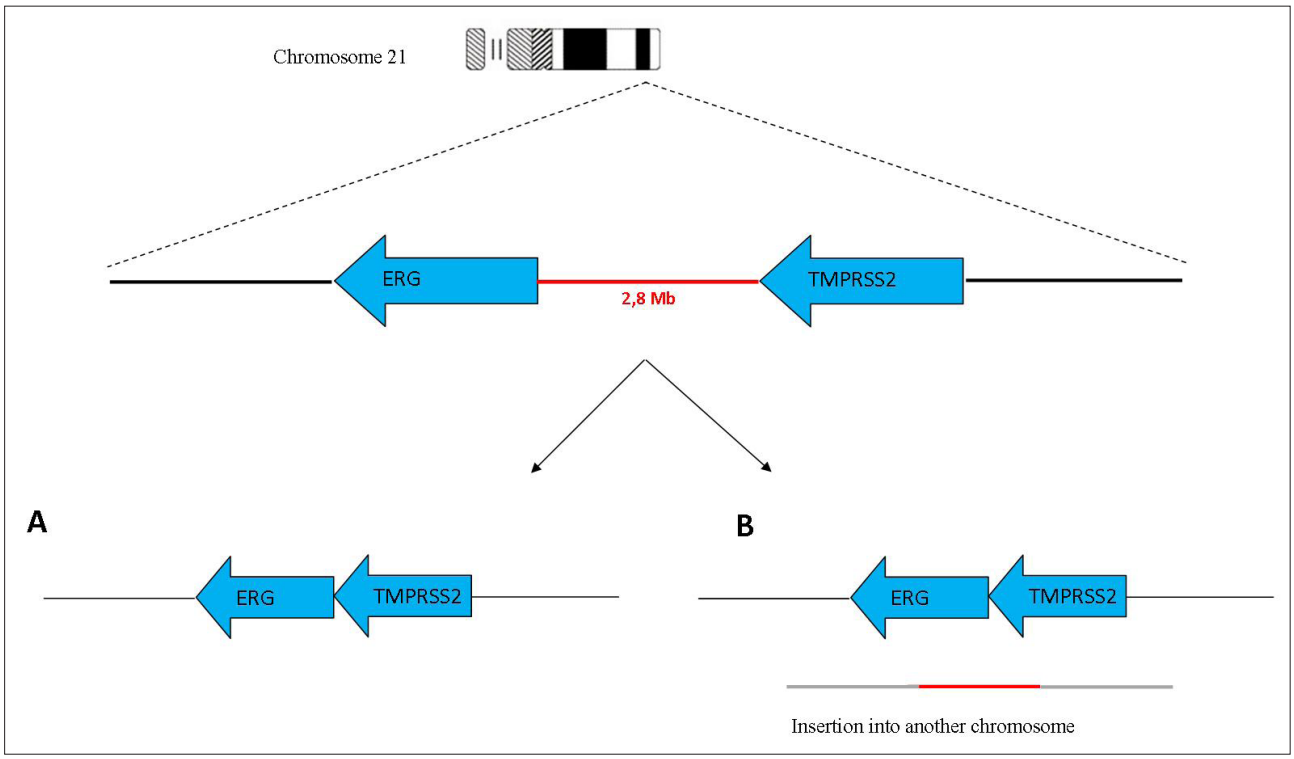

Fig 1. Mechanism of fusion formation. A. The fusion of *TMPRSS2* and *ERG* gene generated by an interstitial deletion, where a region of 2.8 Mb is lost (red line). B. The fusion of *TMPRSS2* and *ERG* gene generated through an insertion of interstitial region into another chromosome in genome.

Androgen-induced TOP2B mediated DSBs are highly recombinogenic and could lead to *de novo* production of *TMPRSS2-ERG* fusion transcripts. TOP2B-mediated DSBs occurring during regulated transcription represents a new paradigm for development of DSBs involved in generating gene rearrangements in cancer[40,41]. On the base of genome-wide linkage analysis, Luedeke et al.[42] found significant association of *TMPRSS2-ERG* fusion-positive PCa and rare variants in the genes *POLI* [Polymerase (DNA Direct) Iota (variant F532S)] and *ESCO1* [Establishment Of Sister Chromatid Cohesion N-Acetyltransferase 1 (variant N191S)]. Both genes encode proteins involved in the repair of DNA DSBs, thereby protecting the chromosomal stability and preventing translocation events such as *TMPRSS2-ERG* fusion.

FUSION TRANSCRIPT ISOFORMS

TMPRSS2-ERG gene fusions are one of the most common genetic events in PCa and account for 80-90% of PCa fusions[6,36,38,43]. Several studies have revealed more than 20 *TMPRSS2-ERG* transcript variants, which arise both as a result of alternative splicing or of recombination mechanisms (e.g. interstitial deletions, insertions, translocations) (ref.[10]). The most common *TMPRSS2-ERG* isoform consists of exon 1 of *TMPRSS2* fused to exon 4 of *ERG*. Heterogeneity has been identified in the location of the *TMPRSS2-ERG* fusion junction and in the exons of *ERG* present in the fusion transcript[4]. Wang et al.[44] showed that both the presence of certain isoforms of *TMPRSS2-ERG* fusion and their expression level, may affect PCa progression. For example, the isoform consisting of exons 1-2 of *TMPRSS2* fused to exon 4 of *ERG* is associated with features of aggressive PCa. Although overexpression of full-length ERG protein promotes the transcriptional activation of oncogenes and facilitates cancer progression, some N-terminal truncated ERG proteins encoded by *TMPRSS2-ERG* fusion genes, might inhibit oncogenic transcriptional activation by competitively binding to ETS domain binding sites in gene fusion positive prostate cancer. PCas expressing these types of truncated ERG proteins might possess less aggressive features[45].

HETEROGENEITY OF TMPRSS2-ERG IN PROSTATE CANCER

The majority of primary PCas arise multifocally[46]. PCa is a heterogeneous group of diseases originating in multiple independent clonal expansions, as confirmed by discordant patterns of allelic loss among various tumor foci[47,48]. Approximately 75% of whole-mount radical prostatectomy specimens have multiple cancer foci. Recently, several groups have examined ETS fusions in the context of multifocal cancer. All groups showed that from 41% to 67% of cases harbor individual cancer foci that differ with regard to the presence or absence of ETS fusions or a fusion mechamism (i.e. rearrangement through deletion or insertion) (ref.[4,31,49-52]). This observed interfocal heterogeneity supports the hypothesis that prostate carcinogenesis may be a multicentric process, in which at least two independent pathogenetic pathways coexist in the same prostate, leading to independent neoplasias with or without the involvement of the ETS pathway[30]. Intrafocal heterogeneity has also been described[32,53,54]. Svensson et al.[53] found cases showing intrafocal heterogeneity (i.e., both rearranged and non-rearranged nuclei in the same cancer focus), and cases where the same gene rearrangement showed both types of rearrangement mechanisms (i.e., rearrangement through insertion and deletion) within the same focus. The molecular heterogeneity may be the result of tumor progression and may lead to different tumor types and clinical outcomes[55].

Several studies have demonstrated the presence of *TMPRSS2-ERG* gene fusion in most cases of metastatic PCas (ref.[37,56,57]). In unifocal PCa, the status of the *ERG* rearrangement was concordant for the primary PCa and metastasis. In multifocal PCa, despite a significant interfocal discordance, the status of the *ERG* rearrangement was concordant for the dominant primary tumor focus and metastasis. The concordance of the *ERG* gene rearrangement status for the dominant primary tumor focus and metastasis suggests that metastasis most likely arises from the dominant tumor focus in multifocal PCa (ref.[58]). In this type of PCa, the dominant tumor focus is usually considered to be biologically most relevant[50]. However, it cannot be excluded that the metastasis may also arise from the secondary focus, particularly in patients whose dominant and secondary tumor foci show a similar pattern of the *TMPRSS2-ERG* gene fusion[58]. Consistent with these findings Mehra et al.[50] report that in 83% of cases, *TMPRSS2-ERG* can be linked to the dominant tumor. However, in 17% of cases, *TMPRSS2-ERG* is seen in secondary tumors. This result also suggests that in a small proportion of cases, the secondary tumors can also have considerable alterations that may be biologically significant. Moreover, Perner et al.[56] also reported that multifocal PCa can demonstrate both *ERG*-positive and *ERG*-negative foci and that the positive foci have a greater predilection for metastasis. This has potential clinical impact on disease progression and therapeutic intervention. On the other hand, Guo et al.[58] found that the metastasis may also arise from the tumor focus without rearrangement of the *ERG* gene in multifocal PCa.

Mehra et al.[37] discovered that *TMPRSS2-ERG* gene fusion in all metastases was associated with deletion of the 5´*ERG* gene. However, Attard[57] and Guo[58] found that *TMPRSS2-ERG* gene fusion in metastases was associated with translocation of the 5´*ERG* gene. Therefore, *TMPRSS2-ERG* gene fusion in metastatic PCa is not exclusively associated with deletion of the 5´*ERG* gene. Different tumor foci of multifocal primary PCa may differ in the presence of *TMPRSS2-ERG* gene fusion and in fusion mechanism, while all metastatic sites display identical ETS rearrangement status (fusion positive or negative), and the same fusion mechanism, when *TMPRSS2-ERG* gene fusion is present.

INTERPLAY OF TMPRSS2-ERG WITH SIGNALLING PATHWAYS

Zong et al.[59] found that increased expression of ETS proteins in adult murine prostate epithelial cells is sufficient to induce epithelial hyperplasia and focal prostatic intraepithelial neoplasia (PIN) lesions, but not progression to carcinoma. *ERG* interacts with alterations in *PI3K* (Phosphatidylinositide 3-Kinases) signalling, such as *PTEN* (Phosphatase And Tensin Homolog) inhibition or *AKT1* (V-Akt Murine Thymoma Viral Oncogene Homolog 1) up-regulation, to cause the development of a well-differentiated adenocarcinoma. Loss of *PTEN* and the presence of the *TMPRSS2-ERG* gene fusion are events significantly associated with PCa (ref.[60,61]). Bismar et al.[62] hypothesize that PCa development may be driven initially by *PTEN* genomic hemizygous loss, causing HGPIN lesions. Monoallelic *PTEN* inactivation leads to genomic instability which may facilitate the chromosomal rearrangement leading to gene fusion formation and progression to cancer. Subsequent biallelic *PTEN* inactivation, by either homozygous deletion or deletion of one allele and mutation of the other, characterizes a particularly aggressive subset of metastatic and hormone-refractory PCas (ref.[63]).

ERG overexpression in PCa is highly implicated in promoting motility and invasiveness, and is associated with elevated levels of *HDAC1* (Histone Deacetylase 1) and subsequent down-regulation of *HDAC1* targed genes, activation of *WNT/β-catenin* signalling pathway and inhibition of apoptotic signalling. *HDAC1* upregulation is common in PCa, but was found to be uniformly increased in tumors with *ERG* rearrangement[9]. Activation of the androgen receptor (AR) through the *WNT/β-catenin* signalling results in increase in AR transcription and expression, enhanced transcription of *TMPRSS2-ERG* and high levels of *ERG* (ref.[64]). Overexpression of AR alone does not stimulate hyperplastic lesions, but when combined with high levels of *ERG*, it promotes the development of more poorly differentiated, invasive adenocarcinomas[59]. Elevated *ERG*, as a result of the *TMPRSS2-ERG* gene fusion, modulates the growth of PCa cells by upregulating the *MYC* oncogene and by abrogating the differentiation of prostate epithelium[65]. Elevated *MYC* expression in primary prostate tumor is biologically relevant and may be a predictor of future biochemical recurrence[66]. *ERG* can shut-down androgen signalling by blocking the AR expression, thereby preventing the normal development of prostate cells. Furthermore, *ERG* induces repressive epigenetic programs via direct activation of the *H3K27* methyltransferase *EZH2* (Enhancer Of Zeste Homolog 2), a member of the Polycomb-group (PcG) family. In this model, *TMPRSS2-ERG* plays a crucial role in cancer progression by disrupting lineage specific differentiation of the prostate and potentiating the *EZH2*-mediated dedifferentiation program[67].

Riberio et al.[68] reported an association of *ERG* expression with expression of several genes encoding metabolic enzymes or extracellular/transmembrane proteins involved in cell adhesion, matrix remodeling or signal transduction pathways. They also observed significant overexpression of *CRISP3* (Cysteine-Rich Secretory Protein-3) in fusion-positive PCas compared with non-malignant tissue or fusion-negative PCas. They further confirmed a strong correlation between *ERG* and *CRISP3* mRNA levels. The presence of *ERG* genomic rearrangement and *ERG* and *CRISP3* mRNA overexpression were both associated with pT3 locally advanced tumors. Ultimately they proved that CRISP3 protein is a direct target of overexpressed *ERG*, suggesting that *CRISP3* may be a mediator of tumor progression driven by the *TMPRSS2-ERG* rearrangement.

TMPRSS2-ERG GENE FUSION AS A PROGNOSTIC MARKER

The prognostic implications of *TMPRSS2-ERG* gene fusion in PCa are still unclear. Since 2005, when Tomlins[6] first described the presence of this fusion in PCa, a large number of studies have been published in this field. Some authors found a correlation between the presence of fusion and poor prognosis[36,44,69-71], but others found a correlation between the presence of fusion and good prognosis[72-74] or no correlation[31,75-78]. The prognostic value of *TMPRSS2-ERG* rearrangements in selected studies is summarized in Table 1. It seems that earlier studies tended to interpret *TMPRSS2-ERG* gene fusion as a marker of poor prognosis and recent large cohort studies as a marker of better prognosis but most of the data suggest a trend towards unfavourable disease outcome in the presence of gene fusion[10]. There are several explanations for these controversial observations such as clinical settings (surgical or other interventions immediately after diagnosis versus conservative management), size of patient cohorts, differences in sample collection and in the technique used for determination of gene fusions[10,79]. Crucial issues are the definitions of study endpoints such as biochemical failure (rise in serum PSA after prostatectomy) versus overall/disease-specific survival[80]. The disconcordant results may also be caused by the actual characteristics of PCa, such as PCa heterogeneity, the presence of the fusion variants and geographical and/or ethnical differences[10].

Attard et al.[71] found that patients with two or more copies of the *TMPRSS2-ERG* fusion gene (due to the interstitial deletion - Edel) had worse survival rates than patients without *TMPRSS2-ERG* rearrangement. This is consistent with the view that *ERG* overexpression is responsible for driving cancer progression, and that the 2.8 Mb deletion (containing genes with tumour suppressor activity) may contribute to the oncogenic potential of the *TMPRSS2-ERG* fusion product[6,36].

In contrast to Attard et al, Gopalan et al.[76] reported that *TMPRSS2-ERG* rearrangement alone was not associated with clinical outcome but with lower grade cancers. These authors described a subgroup of cancers with increased copy number of *TMPRSS2-ERG* loci, which were more clinically aggressive. These PCas were predominantly aneuploid/tetraploid and shared additional chromosomal abnormalities. They therefore concluded that the aggressive clinical behaviour is associated with

Table 1. Prognostic value of TMPRSS2-ERG rearrangements in selected studies.

Biological characteristics	Method of detection	Number of patients	Clinical characteristics	Prognostic association	Ref.
TMPRSS2-ERG through deletion	FISH	118	Clinically localized and advanced PCa (high percentage of men with metastasis and high PSA levels)	Metastases, high tumor stage, higher PSA biochemical recurrence	Perner et al.[36]
TMPRSS2 (exon 2) - ERG (exon 4)	qRT-PCR	59	Clinically localized PCa	Aggressive PCa	Wang et al.[44]
TMPRSS2-ERG, any rearrangement	FISH, qRT-PCR	111	Population-based cohort of men with localized PCa (watchful waiting cohort)	Metastases and death due to the PCa	Demichelis et al.[69]
TMPRSS2-ERG, any rearrangement with PTEN deletion	FISH	125	Primary PCa after radical prostatectomy	Earlier biochemical recurrence of PCa	Yoshimoto et al.[70]
Duplication of TMPRSS2-ERG through deletion	FISH	445	Conservatively manged PCa	Shorter cause-specific survival	Attard et al.[71]
TMPRSS2 (exon 0 or 1) - ERG	qRT-PCR	112	Primary PCa after radical prostatectomy	Longer progression-free survival	Boormans et al.[72]
TMPRSS2-ERG, any rearrangement	FISH, qRT-PCR	150	Untreated primary PCa after radical prostatectomy	Longer progression-free survival	Saramaki et al.[73]
TMPRSS2 (exon 0) - ERG	qRT-PCR	67	Primary PCa after radical prostatectomy	Less-aggressive biological behavior	Hermans et al.[74]
TMPRSS2 (exon 1) - ERG (exon 4 or 5)	qRT-PCR	45	Primary PCa after radical prostatectomy	No correlation	Furusato et al.[31]
TMPRSS2-ERG, any rearrangement	FISH	214	Population-based cohort of men with localized PCa	No statistically significant associations	FitzGerald et al.[75]
TMPRSS2-ERG, any rearrangement	FISH	521	Primary PCa after radical prostatectomy	TMPRSS2-ERG rearrangement alone is not asociated with outcome of PCa. Aggresive clinical features are probably associated with generalized aneuploidy.	Gopalan et al.[76]
TMPRSS2-ERG, any rearrangement	IHC, FISH	2805, 453	Primary PCa after radical prostatectomy	TMPRSS2-ERG fusion is unrelated to PCa phenotype.	Minner et al.[77]
TMPRSS2-ERG, any rearrangement	FISH	344	Primary PCa after radical prostatectomy	Lack of prognostic significance of the ERG fusion by FISH. CNI of ERG, likely as the result of aneuploidy, was strongly predictive of PCa reccurence.	Toubaji et al.[78]

IHC, immunohistochemistry; CNI, copy number increase

increased copy number of chromosome 21 and reflect generalized aneuploidy rather than copy number increase of rearranged *TMPRSS2-ERG*. Findings consistent with this were published by Toubaji et al.[78]. They reported that *TMPRSS2-ERG* gene fusion was not associated with PCa recurrence, supporting the lack of prognostic significance of the *ERG* gene fusion determined by FISH. In contrast, they found that *ERG* gene copy number gain without fusion was associated with twice the risk of PCa recurrence. The *ERG* gene copy number increase is explained as the result of tumor aneuploidy, potentially leading to chromosome 21 polysomy. In this context, the association of greater probability of tumor progression with increased copy number of the *ERG* gene formed without fusion is not surprising given the previous evidence supporting aneuploidy as a negative prognosticator in Pca (ref.[81-83]).

CLINICAL IMPLICATIONS

Serum PSA monitoring is widespread and clinically used for following up PCa development but it has several limitations as an early detection marker[22,84]. The estimated frequency of PSA screening-detected cancers which never manifest as clinical symptoms is 23 to 44% (ref.[85]) but early detection of PCas can increase the curative success rate[86]. Therefore, it is necessary to search for new early biomarkers. Due to PCa heterogeneity, the use of marker panels can further improve the diagnostic and prognostic sensitivity[87,88]. Recently, attention has focused on *PCA3* (Prostate Cancer Antigen 3) a prostate specific noncoding RNA, highly overexpressed in PCa and which may be detected in urine[89]. Many studies have shown that a *PCA3*-based urine test can improve the specificity of PCa diagnosis[90-93]. Similar to *PCA 3*, the *TMPRSS2-ERG* fusion transcript can be detected in urine and this improves PCa diagnostics. *TMPRSS2-ERG* gene fusion analysis in combination with urine *PCA3* analysis enhances the probability of PCa detection. The introduction of new urinary biomarkers *PCA3* and *TMPRSS2-ERG* into clinical practice could lead to a considerable reduction of prostate biopsies[94].

Prostate small cell carcinoma is a relatively rare type of PCa with aggressive clinical outcome. It is difficult to distinguish prostate small cell carcinoma from bladder small cell carcinoma especially in small biopsy samples. Four independent studies showed that the frequency of *ERG* alterations in prostate small cell carcinoma is the same as in adenocarcinoma[95-98]. Thus, *ERG* rearrangement was found in approximately half of tested prostate small cell carcinoma samples, but was not detected in small cell carcinoma of another origin (for example bladder small cell carcinoma or lung small cell carcinoma). Although the sensitivity of this marker is approximately 50%, its predictive value is higher than other markers such as PSA or prostein, which are found only in 28% of cases of prostate small cell carcinoma[99]. Detection of *ERG* rearrangement in small cell carcinoma, and in other epithelial and non-epithelial tumors, clearly confirms the prostatic origin of tumor[80,100].

The *TMPRSS2-ERG* gene fusion in PCa makes it a desirable therapeutic target. It was shown that knockdown of this gene fusion product inhibited primary tumor growth[101]. One recent study reported targeting the *TMPRSS2-ERG* gene fusion junction *in vivo* by specific siRNAs delivered via liposomal nanovectors. This approach resulted in tumor growth inhibition without any apparent toxicity or evidence of the native ERG protein down-regulation[102]. Other approaches include using other inhibiting modulators of ETS transcription such as upstream signalling kinases or downstream targets of ERG protein to block its activity[103]. Importantly, Brenner et al.[104] investigated the mechanisms by which ETS gene fusions mediate their effects, and found that *TMPRSS2-ERG* product interacts with the enzyme PARP1 [Poly (ADP-Ribose) Polymerase 1]. This ETS:PARP1 interaction axis represent a target for therapeutic intervention, and motivates the assessment of ETS gene fusion as a potential predictive biomarker of response in future clinical trials incorporating PARP inhibitors into the treatment of PCa and other ETS fusion-positive malignancies.

CONCLUSION

TMPRSS2-ERG gene fusion appears to be a suitable promising biomarker for its specificity to PCa tissue, high incidence and a connection with the androgenic signalling pathways. The introduction of early and reliable diagnostic markers discriminating PCa could obviate unnecessary biopsies. The combination of prostate specific markers, such as *TMPRSS2-ERG* and *PCA3* may be one way of improving diagnostics. The prognostic significance of the *TMPRSS2-ERG* gene fusion is still unclear to date. However, the occurrence of this gene fusion in small cell carcinoma can be used to determine the prostate origin of the PCa. Finally, several new strategies for therapeutically targeting ETS fusions and their modulators have been identified and are currently being investigated.

ACKNOWLEDGEMENTS

This work was supported in part by grants NT13573 from the Czech Ministry of Health and NPU I LO1304 from the Czech Ministry of Education.

Authorship contributions: AB, JB: literature search and manuscript design; All autors: manuscript drafting and final approval.

Conflict of interest statement: The authors state that there are no conflicts of interest regarding the publication of this article.

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