Fusion transcripts: hopes and pitfalls in tranquilizing the trouble mongers in prostate cancer

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Abstract
Prostate cancer is a multifactorial disease. It harbours a miscellany of fusion transcripts originating from chromosomal rearrangements. Additionally, susceptibility to genomic rearrangements is particularly enhanced in prostate cancer which is triggered by androgen. These fusion transcripts hijack the promoters of androgen regulated genes and exploit them for triggering anomalies. These chimeric transcripts vary in various cancer foci. A complex barcode underlies the heterogeneous response of these entities to stress. Nonetheless these transcripts create a formidable state of affairs within the cell. Exacerbation of the disease which is mediated by fusion transcripts culminates into a poor survival.

Currently there are unsatisfactory and inefficient measures to circumscribe this rapidly growing threat. The review will encompass various mechanistic insights of the androgen receptor mediated genomic instability and the mediators entailed in rendering cell error prone. Moreover efficacy of therapeutic interventions recently designed keeping in view the molecular hierarchy will be evaluated.

Key words: ATM; Prostate cancer; TMPRSS2-ERG

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Received: November 27, 2010
Accepted: January 15, 2011
Published online: February 06, 2011
DOI:10.5455/jeim.060211.rw.001

Introduction
Prostate cancer is a multifaceted and multistep disease. It is a life threatening disease that is undruggable to date because of stumbling blocks in the standardization of therapy. With an addition of substantial fraction of information it is becoming evident that androgen signaling is predominantly mediating disease exacerbation exclusively or synchronously. The complication and criticalities of mechanisms have recently been dismantled to a greater extent. Earlier it was thought that prostate cancer can be clinically managed by ablating androgen. However androgen ablation is unskilled enough to put a stop to disease aggressiveness. Increasing sophisticated understanding has prompted researchers to reinterpret the patterns and hallmarks of the disease. The in-depth evaluation of the molecular determinants will be helpful to counteract this anomaly.

Numerous recent reviews cover different aspects ranging from discovery of fusion transcripts in prostate cancer to various strategies to characterize multiple chimeric transcripts [1-5]. We have attempted in this review to summarize recent findings on various signaling pathways and stimuli leading to chromosomal rearrangements. We gave special emphasis to how various mediators are related to pathophysiology of disease, and carcinogenesis in particular. The review will encompass various mediators at transcriptomics and proteomics that work in concert to promote cancer progression. Fusion transcripts are versatile regulators of derailed genomics. There are an overwhelming number of chimeric transcripts that has been brought to the limelight and the list continues.

Rearrangement: repairing the genome in an unfaithful manner
Prostate cancer is a multi-dimensional molecular anomaly. Recently fusion transcripts have been characterized in prostate cancer tissue. Earlier chimeric transcripts were documented in haematological malignancies. The generation of these transcripts is a result of genome rearrangements. These alterations or rearrangements disturb the individuality of the gene and there is a partial sharing between two genes to carry on the illegitimate dynamics of the neoplastic cell. The chromosomal translocation or genomic rearrangements are generated because of unfaithful repair of the genome after DNA damage. The disruption of genomic stability leads to
oncogenesis. TMPRSS2-ERG is a fusion transcript that is a well documented example of genomic instability outcomes in prostate epithelium. Upcoming sections will unmask the details of these transcripts at molecular basis.

**TMPRSS2: an overview**

A multimeric protein with a serine protease domain was documented [6]. It comprised 492 amino acids, encompassed by 4 domains: serine protease domain harbouring cleavage site at arg or lys residues; Scavenger receptor cysteine-rich (SRCR) domain (specified for engagement with extracellular ligands); LDL receptor class A (LDLRA) domain; alongwith, a domain that spanned the membrane.

It was in 2005 when a research group documented a fusion transcript exclusively expressed in prostate cancer. This fusion transcript was formed because of chromosomal rearrangement and juxtapositioning to another gene of ETS family of oncogenes. ERG and ETV both of these factors belonged to ETS family of oncogenes.TMPRSS2 was fused to either [7].

**ETS: introduction of the team and players**

ETS transcription factors comprise a family having at least 29 different genes divided categorically into 5 subfamilies. These transcription factors have enhanced affinity and therefore bind to the promoter regions of genes having specific DNA sequences. Concomitantly, a co-recruitment of AR and ETS1 at AR promoter targets is also registered. Overexpression of ETS and other family members mediates the translocation of AR into the nucleus. In the absence of androgen and overexpression of ETS there is an enhanced association of ETS with AR that results in a remarkable shuttling of the receptor into the nucleus thus enhancing its dwell time in the nucleus which consequently upregulates the expression of various genes [8]. These factors have a broader implication in a range of pathways together with stem cell development, cellular senescence, uncontrolled proliferation, metastatic dissemination, apoptosis and oncogenesis. ETS are the factors of transcription which contain conserved domain of DNA binding that binds the core DNA sequence. Of the genes known to drive insurrection of prostate biological mechanism, ERG is a member of ‘ERG subgroup’ that is exclusively dissimilar from ‘PEA3 subgroup’. It contains Pnt (pointed) protein interaction domain, whereas ETV1, ETV4 and ETV5 belong to PEA3 subgroup. These are the proteins which are documented in the fusion transcript generation in prostate cancer. Other isoforms are not well documented and data available currently is undeveloped. Normal ERG gene has no less than nine isoforms with several transcriptional initiation sites and alternative exons encoding different proteins. ERG undergoes homodimerization or heterodimerization with ERG isoforms and other ETS family proteins for suppression and interact with the Fos/Jun (AP1; activator protein 1) complex for transcriptional activation of various genes [9-12].

**Genomic rearrangements: partners and partnerships in the crime**

It was earlier presumed that ERG was proto-oncogene that overexpressed recurrently and played an imperative role in exacerbation of the pathology. However, that assumed presumption was underscored when the concept of inter/intra chromosomal rearrangements to the limelight [13]. ETS family is a “double edged sword” that consists of activators and repressors and the activities are triggered in a spatio-temporal manner (Fig. 1).

An additional aspect was observed in fusion transcripts concerning inclusion of exons. Exons 4-7 (of ERG) were outnumbering exons 1 and 2 in transcript analysis. The jigsaw puzzle was resolved through sequencing of cDNA products. They drew a conclusion by the results of sequencing that 5’ ERG gene had been substituted by sequence derivatives of TMPRSS2 gene. TMPRSS2 and ERG gene reside about 3 megabase apart on chromosome 21. The most recurrent and widespread fusion is between 5’ untranslated regions of TMPRSS2 and 3’ ERG [14-19].

![Figure 1. Classification of ETS family](image-url)
Based on the possible multiple fusions, a nomenclature was proposed a research group for signature chromosomal rearrangements [20]. The most widely studied transcript that existed in the patients analyzed for research was of TMPRSS2-ERG. It was observed that there are two isoforms of this chimeric transcript. One had full length prototype ERG paradoxically other isoform lacked ETS gene [21-29].

Tomlins documented recurring genomic rearrangements by closer proximity of the 5' region of TMPRSS2 to ERG, ETV1 or ETV4 in tissues of prostate cancer with outlier expression. While drawing a parallel between fusions of TMPRSS2 to either ERG or ETV, TMPRSS2-ERG fusions are predominant and outnumber TMPRSS2-ETV1/ETV4, on the basis of (outlier) expressions [30, 31].

In 2008 another versatile regulator ETV5 gained its entry into the family. The multiple 5' partners were documented. Despite an increase in the members of ERG they did not outnumber 5' gene fusion partners. Previously, TMPRSS2 was the only described 5' partner of ERG. There was a rapid increase in the list of the members as SLC45A3, HNRPA2B1, and C15orf21, prostate-specific, androgen-induced genes, FLJ35294 and CANT1 were acclaimed as the candidates for genomic fusions. Consistent with the same phenomenon another androgen-insensitive gene, DDX5, was documented that underwent a fusion with ETV4, resulting in a DDX5-ETV4 fusion protein [32-35]. These are detected through circulating tumour cells in urine and blood [36, 37].

**Signal transduction: the mechanistic insights**

The gene encoding androgen receptor (AR), otherwise identified as the dihydrotestosterone receptor, is positioned on the X chromosome. Interaction of DHT to the androgen receptor (AR) dissociates heat-shock proteins (HSPs) from the receptor and promotes phosphorylation. The AR undertakes dimerization and binds to androgen-response elements in the promoter regions of target genes. Co-activators and corepressors also tether to the AR complex, thus modifying the firing rate of the genes by stimulating or inhibiting the activity accordingly. Contrarily, androgen-independent signaling is regulated by the phosphorylation of AR by either AKT or MAPK which are the molecules of growth factor mediated signaling (Fig.2). This phosphorylation activates the receptor and catapults it into the nucleus to switch on the genes in absence of androgen. With reference to growth factor mediated modulation of androgen regulated genes, derailed EGF signaling resulted in expression of STAG/PMEPA/ERG1,2. Thus androgen deprived environment promotes the expression of PMEPA by an outlaw pathway [38].

PMEPA is a negative regulator of pathogenesis and localized to glandular epithelium of prostate. It works in concert with NEDD4, and methylation of the gene in neoplasia highlights the safeguarding attributes of this molecule [39-41]. Meanwhile it dampens the androgen receptor regulated genes by degrading the AR by collaborating with NEDD4 [42]. Another body of evidence indicates that loss of lipid phosphatase PTEN is another way to disease exacerbation, so that PtdIns(3,4,5)P3 can no longer be converted back to its substrate, PtdIns(4,5)P2. AKT activated by PtdIns(3,4,5)P3, serves AR unlawfully by phosphorylating it. It also activates and perpetuates parallel survival pathways by phosphorylating and inactivating pro-apoptotic molecules. SMARCD1/BAF60a and c-Jun also enhance AR transactivation in LNCaP cells, which is equivalent to patterns of expression and growth in hormone-refractory prostate cancer cells. Importantly, siRNA-mediated suppression of c-Jun results in reduced growth of these cells. On the other hand enforced expression of the gene resumed uncontrolled cellular growth. This strongly demonstrates an important biological role for c-Jun in castration resistant prostate cancer [43, 44].

There was an over expression of ETV1 in prostate cancer but nonappearance of fusion transcripts pointed towards lack of chromosomal rearrangements. A clear demarcation exists between androgen dependence and independence [45, 46].

The chimeric transcript has to face collaboration and opposition. The transcript activation is a serious threat to the safeguarding machinery that comprises of PTEN. PTEN plays an important role in dampening the lethality of the consequences. Conversely PTEN is rendered inactive and an activation of AKT and PI3-K orchestrates the pathogenesis. Translational start site was identified in TMPRSS2-ERG fusion [31]. They showed that co-existence and collaboration of TMPRSS2-ERG and PI3-K activation is indispensable to develop prostatic intraepithelial neoplasia. TMPRSS2-ERG fusion and PTEN loss together is a forecaster of disease progression. Moreover activation of AKT and PI3-K strengthens the neoplastic activity of the fusion transcript [47-49].
Insights of current understandings of chromosomal translocations

Normal and tumor cells portray a discriminate androgen signaling pathway. In tumors, the molecular details of commencement of signaling are misrepresented. Androgen regulated promoters are fused to new genes which act as a new target for androgen signaling. There is a reduction of TMPRSS2 expression if prostate cells are TMPRSS2-ERG positive but dissimilarly it does not undergo a decline in the absence of fusion genes [50, 51].

It is well documented that androgen binds to the androgen receptor, this leads to chromosomal translocations. There is a collaboration of AR and some other proteins that work in conjunction to induce genomic rearrangements [52]. TOP2B, AID and GADD undergo co-recruitment with AR for genomic rearrangements [53]. The ligand bound androgen receptor along with genotoxic stress initiates two types of enzymatic activities; activation induced cytidine deaminase and the LINE-1 repeat encoded ORF2 endonuclease. Hence, site specific DNA double stranded breaks (DSBs) are produced at translocation loci which guide this illegitimate re-annealing through NHEJ. This switching towards NHEJ instead of HR is indicative of inactivation of ATM. However a new horizon opened when LNCaP cells pre-treated with DHT underwent DNA double-strand breaks and genomic rearrangements. TMPRSS2-ERG fusions appeared after additional irradiation. Androgen signaling facilitates juxtapositioning of fusion partners that probabilistically stimulates the gene fusion when subjected to agents that cause DNA double-strand breaks. Similarly cells deficient in DNA repair genes are prone to genomic rearrangements [54, 55]. We have recently documented that impairment of ATM results in enhanced genomic rearrangements. Moreover fusion transcripts are upregulated in ATM compromised cells but retrieval of ATM by phytonutrient (EGCG; epigallocatechin gallate) attenuated genomic rearrangements. On a similar note, TGF signaling is implicated in potentiating the activities of ATM. In TGF treated cells ATM was activated but the results were more prominent when negative regulators of TGF signaling were abolished using siRNA [56, 57].

Figure 2.
Testosterone enters cytosol and 5-reductase converts it into dihydrotestosterone (DHT). Ligand receptor engagement induces dissociation of heat-shock proteins (HSPs) and phosphorylation of receptor. AR undergoes dimerization and binds to response elements of target genes. Co-activators (such as ARA70, SMARCD and c-Jun) and corepressors also attach to the AR complex, suppressing or promoting activity, correspondingly. Activation or repression of target genes results in survival of the cell. In the outlaw pathway, receptor tyrosine kinases (RTKs) are activated and the AR is illegitimately served by either the AKT (protein kinase B) or the mitogen-activated protein kinase (MAPK) pathway, producing signal transduction that is the foundation of disease aggressiveness in castration resistant prostate cancer.

AR, androgen receptor; AKT, protein kinase b-alpha; ARA70, androgen receptor coactivator, 70-KD; DHT, dihydrotestosterone; NEDD4, neural precursor cell expressed, developmentally downregulated 4; SLC45A3, solute carrier family 45, member 3; SMARCD1, swi/swr-related, matrix-associated, actin-dependent regulator of chromatin, subfamily d, member 1; TMPRSS2, transmembrane serine protease.
A research group identified some molecular modifications in ERG sequences in specimen of prostate cancer. They observed duplication of 3-prime ERG sequence together with interstitial deletion of 5' ERG sequences. Another variation was with 1 copy of 3' ERG (1Edel) did not have a worse clinical outcome. The findings were in accordance with the hypothesis that fusion of 5' TMPRSS2 to 3' ERG results in overexpression of ERG. Attard et al suggested that molecular analysis of ERG, including duplication may allow categorical characterization of prostate cancer [21-23]. The frequency wise distribution of duplicated fusion was higher in non-minute adenocarcinomas. However there is a contradictory body of evidence that states that comparable rate of TMPRSS2–ERG fusion in minute adenocarcinomas may argue against its value as a marker of aggressive prostate carcinoma phenotype [58].

**Techniques for detection of prostate specific fusion transcripts**

RT-PCR of human prostate tissue is challenging because RT-PCR is, in particular sensitive to interference from machinery interrelated to RNA degradation. It is a well established fact that human prostate tissue depicts very elevated rates of RNase activity and subsequent RNA degradation. FISH evaluates the rearrangement in DNA instead of RNA, but has few limitations in its ability to detect the broad spectrum of possible chromosomal deletion or translocation events that induce closer proximity of TMPRSS2 and ERG. The branched DNA assay described by [59] provided a substitute to RT-PCR or FISH for detecting TMPRSS2-ERG fusion. Branched DNA assay has inter-assay uniformity that compares favorably to that of RT-PCR, and being quantitative, it is dissimilar from FISH assays. In accordance with this assumption, this assay offers broader implications as a diagnostic tool to detect fusions which outdate sensitivity of FISH and RT-PCR thus determining the clinical consequence of this intriguing genetic rearrangement. Earlier attempts to identify truncated ERG products have failed because of lack of specific antibodies. Nevertheless, Park et al established a benchmark by developing a rabbit anti-ERG monoclonal antibody using immunoblot analysis on prostate cancer cell lines, synthetic TMPRSS2-ERG constructs, chromatin immunoprecipitation, and immunofluorescence [60]. ERG protein expression is advantageous in subtyping prostate cancer based on ERG rearrangement status. Sun et al detected TMPRSS2-ETS fusions by a multiprobe fluorescence in situ hybridization assay for the early diagnosis of prostate cancer [61].

In an attempt to diagnosis prostate cancer in an earlier stage, a multiplex model of gene-based, protein-based, and metabolite-based with positive and negative markers in urine has been documented by Cao et al [62]. Stott et al described a high-throughput microfluidic mixing device, the herringbone-chip, or "HB-Chip," which offered comparatively enhanced means for isolation of circulating tumor cells (CTC) [63].

**Therapy: identifying existing challenges**

The interventions for the prostate cancer are unable to checkmate disease refractoriness. Gaze through the molecular lens indicate that androgen receptor holds the key position and the ultimate player engaged in the exacerbation of the disease. There are various routes which have been outlined with reference to AR shuttling into nucleus. Anti-androgens do not prevent AR from shuttling to the nucleus. It prevents AR from stable DNA binding. Only last year, two compounds RD162 and MDV3100 were identified that hampered AR translocation to the nucleus. MDV3100 was effective against androgen receptor (AR) splice variants lacking the ligand binding domain (ARVs). Since the expression of this variant increases acutely in response to androgen withdrawal, this drug provides a strategy to overcome ARV function in the clinic [64-67]. MRP4/ABCC4 is under the control of androgen and is instrumental in prostate cancer progression. It seems intriguing that in various experiments androgen restoration stimulates the expression of this gene yet anti-androgen treatment abolished the expression potentially through an undefined mode of action [68]. So strategies must be designed that can inhibit the translocation of AR into the nucleus. In accordance with this assumption various therapeutic agents might be influential that can retard this trafficking. Silymarin (SM) has been evaluated for its efficaciousness against prostate cancer. The active ingredients were successful in hampering the track of AR [69]. Henceforth it is necessary to address AR and its accompanying proteins that work with striking synergy. Knocking out of ETS family members might be a new avenue to block the distribution of AR in the nucleus. Treatment of androgen-sensitive LNCaP cells with retigeric acid B (RB) and curcumin led to a reduction in the
expression of androgen receptor (AR), and subsequently decreased the transactivity of AR [70, 71].

Androgen signal transduction dampening and potent AR blockers are necessary to limit the saturation of AR in the nucleus [72, 73]. AR function inhibition by blockade of the coactivator groove using an inhibitory peptide is another step of the intercession [74, 75]. A series of biphenylmethylene pyridines has been designed, synthesized and tested as CYP17 and CYP11B1 inhibitors [76]. Cholesterol dysregulation is a culprit that guides cancer progression. Proper execution of novel therapeutic approaches targeting these cholesterol sources might prove as an important factor of combinatorial drug design [77].

On a similar note, AR along with its activators and co-activators in the nucleus is involved in the expression of various cancer favouring genes [78]. An abrogation of various nucleosome remodeling factors might offer exciting horizons. This parameter is considered by Wijngaart et al, who attenuated the expression of various genes by AR by hampering SMARCD1 function [44]. Therefore a detailed analysis of these factors which make the genome responsive to transcription can be a responsible target. Once AR is in the nucleus, there are some characteristic phosphorylation activities triggered by DNA-PK which help AR in populating outside the nucleus. DNA-PK holds dual properties of cancer repressing and promoting activities. Genomic instability is facilitated by DNA-PK on the other hand DNA-PK is actively engaged in decreasing the dwell timespan of AR in the nucleus as increasing or prolonged stay of AR calls for an upregulation of response gene which dictates oncogenesis (B. Paschal; personal communication). SLC45A3-BRAF and ESRP1-RAF are the fusion proteins which are incriminated in the aggressiveness of the disease [79]. These proteins are involved in the activation of mitogen transduction cascade independent of involvement of exclusive RAF proteins. These chimeric proteins can initiate the proxy signalling of RAF which needs upstream RAS protein via ligand receptor engagement extracellularly. A more detailed study is necessary to have a better understanding of the mechanism. Does it influence phosphorylation of AR by ERK as androgen absence calls for phosphorylation of AR via multiple kinases. ERK once switched on triggers shuttling of AR into the nucleus might provide some clues. The inhibitors were used by Palanisamy et al to evaluate the attenuation of the genomic rearrangement [79].

An improved scenario of tumor suppressor genes (TSG) in prostate epithelium might help in aborting the birth of cancer. AT(2)-receptor works in partnership with ATIP portrays an anti-growth factor effect. ATIP expression declines with an increase of the rate of cell growth and androgen-independence. This fall might be because of enhanced degradation of the protein. Henceforth a threshold value of ATIP is essential to mediate the effect of AT(2)-receptor activation to inhibit EGF mediated subversion of biological system. EGF may in part induce cell growth by suppressing the level of ATIP expression. Interestingly EGF itself escapes degradation by inhibiting the expression of REPS2 [80, 81].
Mutations have been found in prostate cancer patients, but usually such mutations increase activity of AR by being responsive to non-androgenic ligands (such as cortisol) or even anti-androgens. RNAi experiments have been (successfully) performed in various manuscripts. It has lately been found that inhibition of 15-hydroxy-prostaglandin dehydrogenase (HPGD) as result of TMPRSS2-ERG overexpression prevents PGE2 catabolism that results in uPA activation and uncontrolled cell growth, contributing to prostate carcinogenesis. Furthermore over expression of fusion transcripts results in upregulation of NFKB target genes (TLR3 and TLR4). TLR4 enhances phosphorylation of serine 536 of p65 thus resulting in high-grade prostatic intraepithelial neoplasia (Fig.3) [82, 83]. Unraveling these paradoxes will enable the researchers to speed up the journey of therapeutic agents from bench to the bedside.

Conclusion and future directions

There is a paradigm shift in the current understandings of the prostate cancer biology after milestone work of Tomlins et al [7]. Although a bit strange and intriguing but poses a serious threat to the dynamics of the cell. This breakthrough drew attention of the researchers towards fusion transcripts. The underpinnings of chromosomal rearrangements advocated various unexplored aspects. Even though there are expanding highways and byways of chimeric transcripts but desperate desire for effectual drug design cannot be overlooked. Keeping in view the preliminary teething stages of prostate therapy, there is an urgent need to scrabble and turn up with positive clinical outcomes.

Despite the fact that prostate cancer is a detrimental discrepancy, interventions to address this invincible disease are not impressive. The pattern of genomic rearrangement is paramount to outline the key players mediating oncosogenesis.

Facts and figures promptly pinpoint the role of oxidative stress and double stranded break in genomic arrangement. This is an alarming situation as the chemotherapeutic drugs which induce apoptosis via double strand breaks are inapplicable because the administration will worsen the results.

Although a general androgen signaling mechanism has been brought from shadow to the limelight, yet there are existing gaps and outstanding questions in terms of alternate transduction cascades that crosstalk at various levels that underlie castration resistant stage. Moreover variation in the transcriptome must be given utmost significance while trying to get a step closer to personalized therapy.

Acknowledgements

We would like to pay sincere thanks to our friend Dr. Dennis J. van de Wijngaart (Department of Pathology, Josephine Nefkens Institute, Erasmus MC, Rotterdam, Netherlands) for his helpful suggestions during the structuring of the review.

Abbreviations

AID: activation-induced cytidine deaminase
AP1: activator protein 1
ARA70; androgen receptor coactivator, 70-KD
AT(2); Angiotensin II receptor
ATIP; AT interacting protein
BAF60a; BRG1-associated factor, 60-kd
BRAF; v-raf murine sarcoma viral oncogene homolog b1
C15orf21; chromosome 15 open reading frame 21
CANT1; calcium-activated nucleotidase
CYP17; cytochrome p450, family 17
CYP11B1; Cytochrome p450, subfamily XI B
polypeptide 1
DDX5; dead/h box 5
DNA PK; DNA dependent Protein Kinase
ERG; V-ets avian erythroblastosis virus E26 oncogene homolog
ERK; extracellular signal-regulated kinase
ESRP1; epithelial splicing regulatory protein
ETV; ETS translocation variant 1
ETS; v-ets avian erythroblastosis virus e26 oncogene homolog 1
FISH; fluorescence in situ hybridization
Fos; v-fos murine osteosarcoma viral oncogene homolog
GADD; growth arrest- and DNA damage-inducible gene
HNRPA2B1; heterogeneous nuclear ribonucleoprotein A2/B1
Jun; v-jun avian sarcoma virus 17 oncogene homolog LINE-1; long interspersed repetitive element-1
LNCaP; lymph node carcinoma of the prostate
MRP4/ABCC4; ATP-binding cassette, subfamily c, member 4
NHEJ; non homologous end joining
NFKB; nuclear factor kappa B
P13-K; phosphoinositide 3-kinase
PMEPA; prostate transmembrane protein, androgen induced 1
PTEN; phosphatase and tensin homolog
PtdIns(3,4,5)P3; phosphatidylinositol trisphosphate
PtdIns(4,5)P2; phosphatidylinositol biphosphatase
REPS2; RALBP1 associated Eps domain containing 2
STAG; synonym for PMEPA
TLR; toll like receptor
TMPRSS2; transmembrane protease, serine 2
TOP2B; topoisomerase 2 B
uPA; urokinase plasminogen activator

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