Characterization of *TMPRSS2*-ETS Gene Aberrations in Androgen-Independent Metastatic Prostate Cancer

Rohit Mehra,[1,2,5] Scott A. Tomlins,[1,2] Jianjun Yu,[1,2] Xuhong Cao,[1,2] Lei Wang,[1,2] Anjana Menon,[1,2] Mark A. Rubin,[6] Kenneth J. Pienta,[3,4,5] Rajal B. Shah,[1,2,3,5] and Arul M. Chinnaiyan[1,2,3,5]

[1]Michigan Center for Translational Pathology, Departments of [2]Pathology, [3]Urology, and [4]Internal Medicine, and [5]Comprehensive Cancer Center, University of Michigan Medical School, Ann Arbor, Michigan; and [6]Department of Pathology and Laboratory Medicine, Cornell University, New York, New York

Abstract

Recurrent gene fusions between the androgen-regulated gene *TMPRSS2* and the ETS transcription factor family members *ERG, ETV1*, and *ETV4* have been identified as a critical event in prostate cancer development. In this study, we characterized the prevalence and diversity of these rearrangements in hormone-refractory metastatic prostate cancer. We used a fluorescence *in situ* hybridization (FISH) split probe strategy to comprehensively evaluate *TMPRSS2*-ETS aberrations across 97 nonosseous metastatic sites of prostate cancer from 30 rapid autopsies of men who died of androgen-independent disease. Tissue microarrays were constructed representing multiple metastatic sites from each patient, and split signal FISH probes for *TMPRSS2, ERG, ETV1*, and *ETV4* were used to assess for *TMPRSS2*-ETS rearrangements. In patients exhibiting these aberrations, multiple sites from an individual case harbored the same gene fusion molecular subtype suggesting clonal expansion of disease. The most common prostate cancer gene fusion, *TMPRSS2-ERG*, can be generated by the mechanism of interstitial deletion (Edel) about 39% to 60% of the time in clinically localized disease. Interestingly, we observed that all of the androgen-independent metastatic prostate cancer sites harboring *TMPRSS2-ERG* were associated with Edel. These findings suggest that *TMPRSS2-ERG* with Edel is an aggressive and, in this study, uniformly lethal molecular subtype of prostate cancer associated with androgen-independent disease. [Cancer Res 2008;68(10):3584–90]

Introduction

The majority of prostate cancer deaths are attributed to metastatic dissemination of the primary tumor. Androgen ablation is initially effective in the management of metastatic prostate cancer; however, most patients develop an androgen-independent state that is invariably fatal (1). To elucidate the biology of prostate cancer progression and metastasis, we have developed a "rapid" or "warm" autopsy program at the University of Michigan composed of patients that died of androgen-independent metastatic prostate cancer. Tumors are collected from metastatic sites and the prostate, when present, and thus constitute a valuable resource to study the natural history and evolution of prostate cancer (2, 3).

We recently identified the fusion of the 5′-untranslated region of *TMPRSS2* (21q22.3) with the ETS family members *ERG* (21q22.2), *ETV1* (7q21.2), or *ETV4* (17q21) in prostate cancer (4, 5) that has subsequently been confirmed by multiple groups (6–9). More recently, we have identified several 5′ fusion partners, supporting the existence of additional molecular subtypes of ETS gene fusions (10). We also showed that most prostate cancers harboring gene rearrangements can be identified using a 5′ and 3′ split probe fluorescence *in situ* hybridization (FISH) strategy with probes tightly flanking the *TMPRSS2, ERG, ETV1*, and *ETV4* loci (4, 5, 11). Using this approach, 65% of clinically localized prostate cancers showed *TMPRSS2* rearrangement, with the majority (55%) being fused to *ERG* (11). Additionally, as *TMPRSS2* and *ERG* are located ~3 Mb apart on chromosome 21, the rearrangement between them occurs either through a translocation between chromosome 21s or by an interstitial deletion (6, 8). Further, in our recent study of multifocal prostate cancers, the majority (70%) of cases showed heterogeneous *TMPRSS2* gene rearrangements between different tumor foci, thus supporting multifocal prostate cancer as a heterogeneous group of diseases (12). Similar observations were reported by Clark and colleagues (13). We have also shown the oncogenic potential of ETS fusions through *in vitro* and *in vivo* expression of *ETV1* (10) and *ERG* (14).

It is currently unknown to what extent lethal androgen-independent metastatic prostate cancers exhibit gene rearrangements or whether they harbor them uniformly at different metastatic sites. Hence, we sought to characterize the frequency, mechanism, and significance of *TMPRSS2*-ETS aberrations in a rapid autopsy cohort of 30 American men who died of androgen-independent metastatic prostate cancer.

Materials and Methods

Rapid autopsy tissue procurement and tissue microarray construction. The autopsies were conducted as previously described (2, 3), and they are referred to as rapid or warm because of the short average interval of 3 h between death of patient and onset of autopsy. A tissue microarray was constructed from 30 rapid autopsies representing all metastatic prostate cancer sites and tumor in the prostate (when present; that is, no prior radical prostatectomy). The rapid autopsy program is approved by the University of Michigan Institutional Review Board and supported by Specialized Program of Research Excellence (National Cancer Institute grant CA 69568).

Fluorescence *in situ* hybridization. We used previously documented 5′ and 3′ split probe strategy to detect *TMPRSS2, ERG, ETV1*, and *ETV4* rearrangements (Fig. 1*A*; ref. 11). Interphase FISH was performed as previously described (4, 5, 11). Slides were examined using an ImagingZ1 microscope (MetaSystems; Carl Zeiss). FISH signals were scored manually (100× oil immersion) in morphologically intact nuclei by two pathologists (R.M. and R.B.S.), and a minimum of 50 cancer cells from each site was recorded. Cancer sites with very weak or no signals were recorded as

Note: Supplementary data for this article are available at Cancer Research Online (http://cancerres.aacrjournals.org/).

R.B. Shah and A.M. Chinnaiyan share senior authorship.

Requests for reprints: Arul M. Chinnaiyan, Department of Pathology, University of Michigan Medical School, 1400 East Medical Center Drive, 5316 CCGC, Ann Arbor, MI 48109-0602. Phone: 734-615-4062; Fax: 734-615-4498; E-mail: arul@umich.edu.

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doi:10.1158/0008-5472.CAN-07-6154

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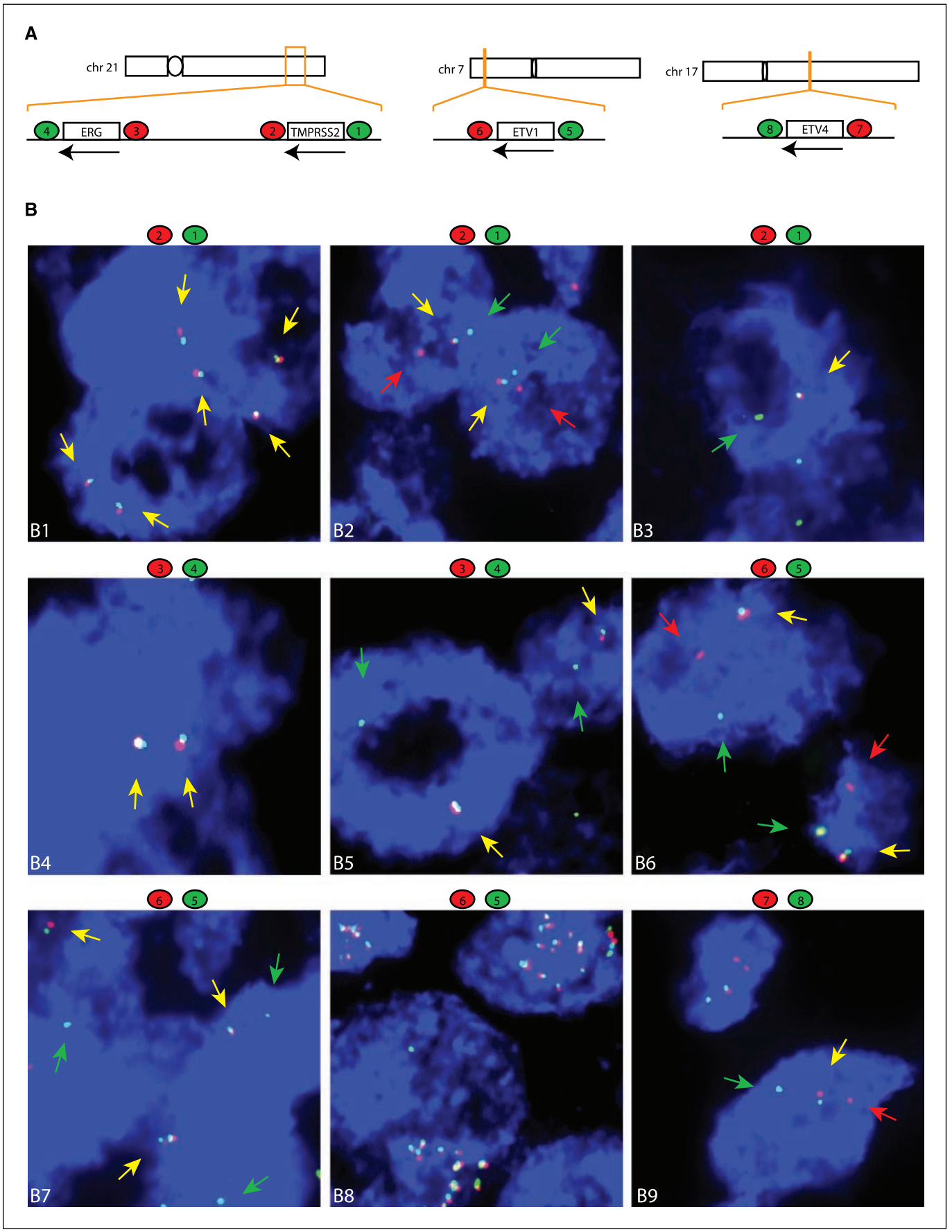

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insufficiently hybridized. Only the nonosseous metastatic sites were evaluated during this study; osseous metastatic sites were nonhybridizable due to dense bone structure and hence excluded.

A cancer site was considered positive for a gene aberration when the tumor showed a rearrangement for any of the split probes mentioned above (through split or deletion; Fig. 1*B*). A metastatic site was labeled as positive for fusion when *TMPRSS2* rearrangement (through split or deletion) was concomitant with a rearrangement (through split or deletion) in any of its known 3′ partners: *ERG, ETV1*, or *ETV4* (10, 11).

Results and Discussion

This University of Michigan rapid autopsy cohort represents patients who died of androgen-independent metastatic prostate cancer (3). Of this group, 28 of the 30 men were initially diagnosed with clinically localized prostate cancer but later developed widely disseminated disease within 5 to 10 years. These patients exhibited progression to lethality despite the use of multiple therapeutic regimens (Supplementary Table S3). In the context of our initial discovery of *TMPRSS2*-ETS fusions in prostate cancer (4, 5, 11), we sought to perform a detailed characterization of these gene aberrations in androgen-independent metastatic prostate cancer.

Our FISH split probe strategy (Fig. 1*A*) revealed gene aberrations in 52% of the rapid autopsy cases. Overall, 48%, 37%, 11%, and 4% of the cases were positive for *TMPRSS2, ERG, ETV1*, and *ETV4* split probe assays, respectively (Figs. 1 and 2). As observed in clinically localized disease (6, 7–9, 15), *TMPRSS2-ERG* fusion was the most common abnormality identified in hormone-refractory metastatic prostate cancer (37%). Additional fusions that were present included *TMPRSS2-ETV1* (case 26) and *TMPRSS2-ETV4* (case 8). In two cases, *ETV1* was rearranged with an unknown partner [cases 4 and 23; the unknown partner in case 23 was recently identified to be *C15orf21* in an independent study (10)]. Case 30 was found to be amplified with multiple (seven to nine) copies of *ETV1* present in each nuclei. Figure 1*B* displays representative FISH images of the diversity of aberrations observed in this cohort.

To determine if the same gene rearrangement is shared across metastatic sites in these subjects, we examined 97 tumor foci from different organs as well as the prostate (when present) with the FISH split probe assays. Interestingly, we found that different metastatic cancer foci within an individual patient harbored the same gene aberration (Fig. 2*B*). Furthermore, the same gene rearrangement exhibited by the metastatic sites was present in tumor in the prostate (when available), as in case 24 (Figs. 2*B* and 3*A*). Similarly, cases without *TMPRSS2*-ETS rearrangements were uniformly negative across all metastatic sites (Fig. 2*B*). The exception to this was case 13, which harbored a *TMPRSS2-ERG* rearrangement at metastatic foci within liver, lung, dura, and soft tissue. However, in this patient, metastatic tumor in liver also displayed a deletion of the 5′ end of *ETV1*, suggesting the possibility of a secondary rearrangement acquired during the evolution of metastatic prostate cancer at this site (Fig. 2*A* and *B*). Although multifocal prostate cancer may harbor different foci that may be *TMPRSS2*-ETS positive or negative (12, 13), our study suggests that a single clone evolves from clinically localized disease to seed the metastatic sites with cells harboring the same ETS gene rearrangement (Fig. 3*B*).

TMPRSS2-ERG gene rearrangement in metastatic disease is similar to what has been observed in clinically localized disease (6–9, 11). In our University of Michigan cohort, we observed *TMPRSS2-ERG* gene rearrangements in 54% of clinically localized prostate cancer (11) and 37% in metastatic disease. In clinically confined disease, 39% of *TMPRSS2-ERG* gene fusions are through intrachromosomal deletion (Edel), whereas 61% are not (and thus presumably caused by translocation of chromosome 21s). By contrast, 100% of androgen-independent prostate cancers harboring the *TMPRSS2-ERG* gene fusion (10 out 10 subjects and 29 of 29 metastatic sites) exhibit Edel (Fig. 2).

Taken together, this is the first study that comprehensively characterizes *TMPRSS2*-ETS aberrations in end-stage, androgen-independent metastatic prostate cancer. Based on our split probe strategy (11), we found that 52% of the cases in this cohort harbored *TMPRSS2*-ETS rearrangements. This frequency (52%) is similar to the 65% frequency of gene aberrations reported by our group for clinically localized prostate cancer (11) and in agreement with other reports in U.S. prostatectomy cohorts (9, 16). This indicates that the high frequency of *TMPRSS2*-ETS aberrations in clinically localized prostate cancer is maintained during progression to an androgen-independent metastatic state. Overall, *TMPRSS2* was rearranged in 48% of the cases (Fig. 2). Gene fusions between 5′ *TMPRSS2* and 3′ *ERG* were the most frequent form (37%) of *TMPRSS2*-ETS rearrangement in androgen-independent prostate cancer, similar to the 40% to 55% previously reported in clinically localized prostate cancers (6, 9, 11, 17). The low frequency of *TMPRSS2-ETV1* (3%) and *TMPRSS2-ETV4* (3%) is also comparable with previous reports (11, 16).

As *TMPRSS2* and *ERG* are in close proximity (3 Mb) on chromosome 21, interstitial deletion between these two genes is a common mechanism of *TMPRSS2-ERG* fusion in prostate cancer (6, 8, 18). In our previous study of clinically localized prostate cancers and *TMPRSS2-ERG* rearrangements in American men treated with radical prostatectomy, 39% were fused through deletion of 5′ end of ERG (11). Likewise, Perner and colleagues (6) showed intronic deletions between *ERG* and *TMPRSS2* resulting in *TMPRSS2-ERG* fusion in 60% of clinically localized cancers and 41% of hormone-naive lymph node metastasis. Despite comparable frequencies of *TMPRSS2-ERG* rearrangement in end-stage, androgen-independent prostate cancer and clinically localized and hormone-naive prostate cancers, the mechanism of rearrangement between them is strikingly different. In comparison with clinically

Figure 1. FISH probe design and representative *TMPRSS2*-ETS chromosomal aberrations detected in androgen-independent metastatic prostate cancer. *A,* for all assays, the chromosomal location of the gene is indicated (*boxes*), with the direction of transcription indicated by the arrow. The 5′ and 3′ bacterial artificial chromosomes (BAC) are indicated in ovals, with the number identifying each respective BAC and the color indicating the probe color in the accompanying images. *B,* representative FISH images of the various *TMPRSS2*-ETS aberrations observed in this study. *Green* and *red arrows,* individual signals; *yellow arrows,* colocalized signals in 4′,6-diamidino-2-phenylindole–stained nuclei. *B1,* colocalized signals in metastatic prostate cancer cells in a case lacking *TMPRSS2* rearrangement. *B2, TMPRSS2* rearrangement positive case without Edel, as indicated by split 5′ and 3′ signals. *B3, TMPRSS2* rearrangement positive case with Edel, as indicated by one pair of colocalized signals (*yellow arrow*) and the loss of one red-labeled probe 3′ to TMPRSS2. *B4,* colocalized signals (*yellow arrows*) in a representative case lacking *ERG* rearrangement. *B5,* an *ERG* rearrangement positive case with Edel showing loss of one red-labeled probe 5′ to *ERG. B6, ETV1* rearrangement positive case without deletion, as indicated by split 5′ and 3′ signals (*green* and *red arrows*). *B7, ETV1* rearrangement positive case with deletion exhibiting loss of one red-labeled probe 5′ to *ETV1. B8, ETV1* amplification shown by multiple (seven to nine) copies of colocalized signals in case 30. *B9,* a case showing rearrangement of *ETV4*, as indicated by break-apart probes. Numbered BACs are as follows: *1,* RP11-35C4 (5′ to *TMPRSS2*); *2,* RP11-120C17 (3′ to *TMPRSS2*); *3,* RP11-95I21 (5′ to *ERG*); *4,* RP11-476D17 (3′ to *ERG*); *5,* RP11-661L15 (5′ to *ETV1*); *6,* RP11-124L22 (3′ to *ETV1*); *7,* RP11-100E5 (5′ to *ETV4*); and *8,* RP11-436J4 (3′ to *ETV4*).

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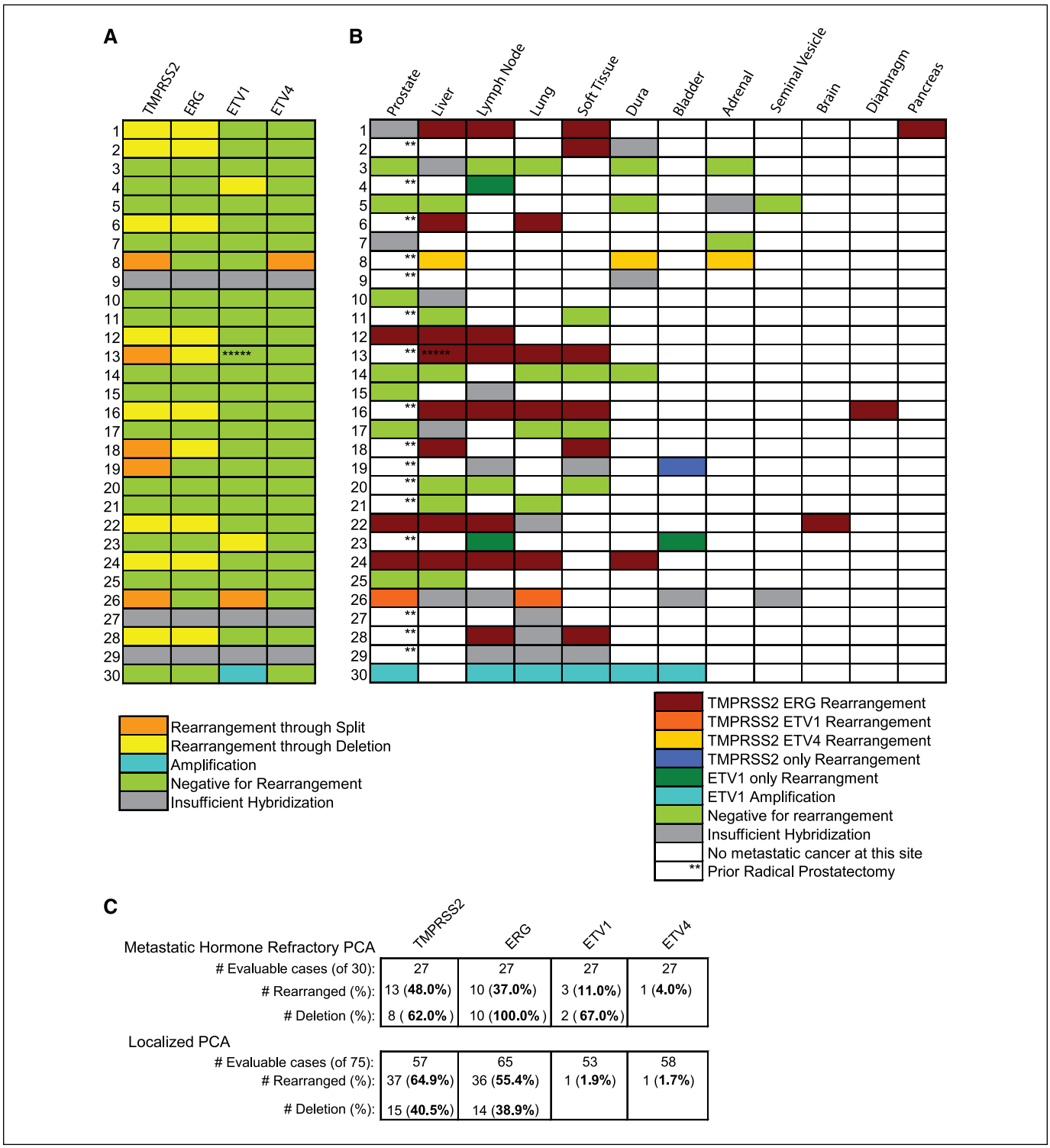

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	TMPRSS2	ERG	ETV1	ETV4
Metastatic Hormone Refractory PCA				
# Evaluable cases (of 30):	27	27	27	27
# Rearranged (%):	13 (**48.0%**)	10 (**37.0%**)	3 (**11.0%**)	1 (**4.0%**)
# Deletion (%):	8 (**62.0%**)	10 (**100.0%**)	2 (**67.0%**)	
Localized PCA				
# Evaluable cases (of 75):	57	65	53	58
# Rearranged (%):	37 (**64.9%**)	36 (**55.4%**)	1 (**1.9%**)	1 (**1.7%**)
# Deletion (%):	15 (**40.5%**)	14 (**38.9%**)		

Figure 2. Diversity of *TMPRSS2* and ETS rearrangements in androgen-independent metastatic prostate cancer. *A,* heat map representation of the *TMPRSS2* and ETS aberrations in metastatic prostate cancers characterized in each subject. *B,* heat map representation of *TMPRSS2* and ETS rearrangement status of the metastatic sites and residual tumor in the prostate (when present) as evaluated in this cohort. **, prostate cancer tissues could not be procured at the time of autopsy because of previous radical prostatectomy and hence were not available for evaluation. No cancer focus was hybridizable for FISH probes in cases 9, 27, and 29. *****, case 13, which harbored a *TMPRSS2-ERG* rearrangement at metastatic foci within liver, lung, dura, and soft tissue liver, also showed a deletion of 5′ end of *ETV1* in metastatic tumor within liver (presumably a nonspecific secondary aberration). Color legend signifies respective aberrations. *C,* table of results for rearrangements in *TMPRSS2, ERG, ETV1*, and *ETV4* as detected by the assays shown in Fig. 1. In this cohort, 27 of 30 cases were evaluable for at least one assay in various metastatic prostate cancer (*PCA*) sites in this cohort, and the number of evaluable cases for each assay is indicated. The percentage (of evaluable cases for that assay) and number of cases with rearrangements for each assay are listed. For *TMPRSS2, ERG, ETV1*, and *ETV4*, the percentage (of rearrangement positive cases) and number of cases with assays consistent with intrachromosomal deletion between *TMPRSS2* and *ERG* are given. The bottom panel contains a comparison of similar assays in a clinically localized prostate cancer cohort we previously evaluated (11). The number and percentage of cases with rearrangements for each assay are given, as well as the number and percentage of *TMPRSS2* and *ERG* rearrangement positive cases with interstitial deletion.

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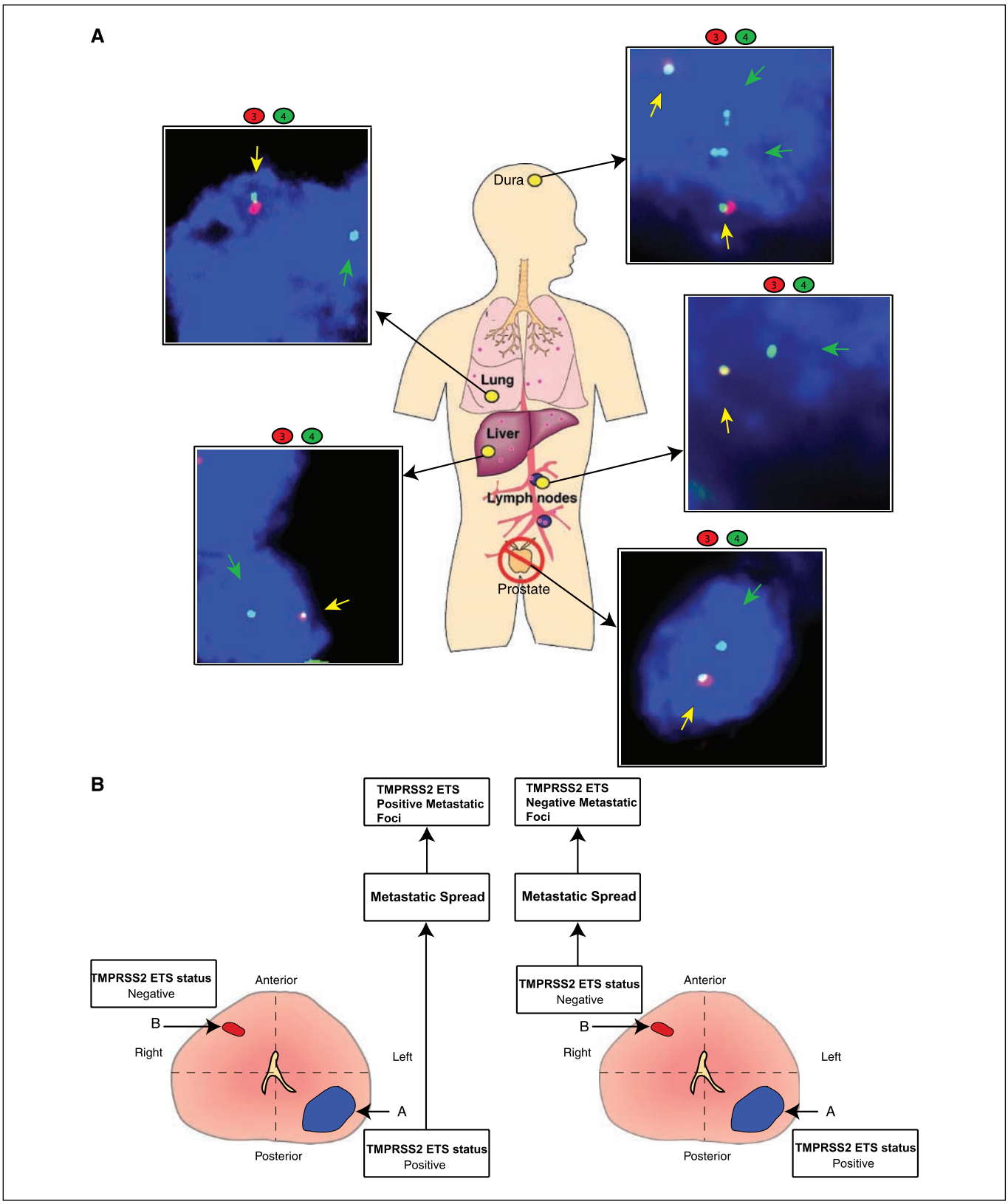

Figure 3. The clonal nature of *TMPRSS2*-ETS aberrations in the spread of metastatic prostate cancer. *A,* representative case 24 of metastatic prostate cancer highlighting the clonal nature of cells harboring *TMPRSS2*-ETS gene fusions. In this case, the subject harbored *TMPRSS2-ERG* with Edel in the prostate and metastatic sites in the liver, lung, dura, and lymph node [representative FISH images from each site are shown; using the multicolor FISH probe strategy, a nucleus with an *ERG* deletion shows replacement of one juxtaposed red and green signal pair with a single green signal representing loss of the 5′ end (red probe)]. *B,* this schematic depicts that although multifocal prostate cancer might harbor *TMPRSS2*-ETS gene fusion–positive nodes and gene fusion–negative nodes, only one "clone" or molecular subtype will progress and result in androgen-independent metastatic disease.

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localized cancer and hormone-naive metastases, *ERG* rearrangement in androgen-independent metastatic prostate cancers occurred exclusively through intrachromosomal deletion (100%). This suggests that prostate cancers with *ERG* fusion due to 5′ deletion harbor an aggressive molecular subtype that is susceptible to higher recurrence, evolves into an androgen-independent state, and eventually progresses to metastasis. Other studies have documented the association of *ERG* fusions with a poor outcome (6, 18–20). Perner and colleagues (6) reported a significant association between clinically localized and hormone-naive locally advanced prostate cancers with *TMPRSS2-ERG* rearrangement through deletions and higher tumor stage and the presence of positive pelvic lymph nodes. Similarly, Attard and colleagues (18) showed that patients with 5′ *ERG* deletion had a significantly worse cause-specific and overall survival. In this study, the presence of an identical *ERG* 5′ deletion in primary cancer within the prostate (when available) and all the metastatic sites from same individual strongly indicates that this molecular aberration occurred at the stage of localized disease before progression to a metastatic state (case 24, Fig. 3*A*). Future studies will investigate the mechanism behind a preferential selection of *ERG*-deleted (Edel) clinically localized prostate cancers to progress into an androgen-independent phenotype.

This study shows and characterizes a common gene rearrangement underlying localized prostate cancer and multiple androgen-independent metastatic foci in an individual patient (Figs. 2*B* and 3*A*). Our results showed that a unique clone of malignant cells in the prostate disseminated to seed different metastatic sites. Further, an aberrant clonal phenotype, acquired by clinically localized cancer, maintained its unique identity as the cancer metastasized, as shown by the consistent presence of *TMPRSS2*-ETS throughout metastatic foci. Thus, it is apparent that malignant cells from a single focus undergo clonal expansion and systemic dissemination to give rise to metastatic deposits in advanced prostate cancer. Such aberrations are presumably a primary initiating event, not secondarily accrued, because they are uniform across metastatic cancer foci. These findings support previous studies that suggested that untreated metastatic tumors contain the bulk of chromosomal alterations necessary for recurrence and eventual spread during antihormonal treatment (21).

Prostate cancer is usually a multifocal disease with considerable histologic, biologic, and molecular variations between different tumor foci (22). In our recent evaluation of multifocal prostate cancers, the majority of cases (70%) had heterogeneous *TMPRSS2* gene rearrangements between different tumor foci suggesting independent clonal expansion (12). The histologic, immunophenotypic, and molecular heterogeneity is persistent when prostate cancer progresses to an androgen-independent phenotype (3). Despite the known heterogeneity of primary and advanced prostate cancers, we remarkably show identical *TMPRSS2*-ETS aberrations in all the metastatic samples and primary prostate cancer (when available) within a single individual patient. This strongly suggests that, although primary nodes of multifocal prostate cancers arise through separate clonal expansion, metastatic cancer arises through clonal expansion of malignant cells from a unique primary focus capable of dissemination. Our findings indicate that if a gene fusion–positive cancer focus spreads from the prostate, the same clone is preferentially seeded across various organs to produce identical gene fusion characteristics. Similarly, all the metastatic foci are uniformly negative for these aberrations in *TMPRSS2*-ETS–negative primary prostate cancers (Fig. 3*A* and *B*).

Further, to investigate the relationship between androgen receptor (AR) and *TMPRSS2*-ETS aberrations, we examined AR immunohistochemical staining status for multiple sites of these 30 rapid autopsy cases (as shown in Supplementary Table S1). We did not observe any significant correlation between AR median staining and *TMPRSS2*-ETS or *TMPRSS2-ERG* rearrangements. Similar to AR immunohistochemical data, *TMPRSS2*-ETS and *TMPRSS2-ERG* aberrations also did not correlate with AR mRNA expression (Supplementary Table S2). Hierarchical clustering of direct AR target genes yields similar patterns for cases with and without *TMPRSS2*-ETS rearrangements (Supplementary Fig. S1*A*). This suggests that alternate mechanisms may be in play to maintain *TMPRSS2*-ETS expression in hormone-refractory prostate cancer. In a recent study, Hermans and colleagues (23) identified cases of androgen-independent metastatic prostate cancer that harbored *TMPRSS2-ERG* fusions at the genomic level [as identified by array comparative genomic hybridization (aCGH)] but did not express *TMPRSS2-ERG* fusion transcripts, leading them to suggest that ETS gene fusions are highly relevant in androgen-dependent metastatic cancer but are bypassed in androgen-independent disease. Our results suggest that bypass of gene fusions may occur in some cases; however, many androgen-independent metastatic prostate cancers with *TMPRSS2*-ETS fusion as evidenced by aCGH or FISH strongly express fusion transcripts. For example, in our original report (4), both the index *TMPRSS2-ERG* (MET28; case 28 in the present cohort) and *TMPRSS2-ETV1* (MET26; case 26 in the present cohort) cases were androgen-independent cancers that strongly overexpressed *ERG* or *ETV1*, respectively.

In summary, *TMPRSS2*-ETS rearrangements in end-stage, androgen-independent prostate cancers provide strong evidence that *ERG* fusion through deletion represents an aggressive molecular subtype of prostate cancer with a high susceptibility to evolve into androgen-independent metastatic state. This study provides compelling evidence that metastatic prostate cancer arises through clonal expansion of a single focus of primary prostate cancer. Insight into the biology of these rearrangements will allow novel therapeutic regimens to be tailored to a susceptible molecular subtype of poor outcome cases.

Disclosure of Potential Conflicts of Interest

The University of Michigan has filed a patent on ETS gene rearrangements in prostate cancer, on which R. Mehra, S.A. Tomlins, M.A. Rubin, and A.M. Chinnaiyan are coinventors, and the diagnostic field of use has been licensed to Gen-Probe Inc. Gen-Probe has not played a role in the design and conduct of the study, in the collection, analysis, or interpretation of the data, or in the preparation, review, or approval of the article. A.M. Chinnaiyan serves as a consultant to Gen-Probe Inc. The other authors disclosed no potential conflicts of interest.

Acknowledgments

Received 11/8/2007; revised 2/4/2008; accepted 2/25/2008.

Grant support: Department of Defense grants PC040517 (R. Mehra) and W81XWH-06-1-0224, NIH Prostate Specialized Program of Research Excellence grants P50CA69568 and R01 CA102872, Early Detection Research Network grant UO1 CA111275-01, and Prostate Cancer Research Foundation. A.M. Chinnaiyan is supported by a Clinical Translational Research Award from the Burroughs Welcome Foundation. S.A. Tomlins is supported by a Rackham Predoctoral Fellowship and is a Fellow of the Medical Scientist Training Program. X. Cao and A.M. Chinnaiyan are investigators of the Howard Hughes Medical Institute.

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We thank Jill Granger for editorial review of this manuscript and Michele LeBlanc, Alan Burgess, and Bo Han for technical support.

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Cancer Res 2008;68:3584-3590.

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