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Considering race and the potential for ERG expression as a biomarker for prostate cancer

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Abstract

Genomic rearrangement and overexpression of the *ERG* oncogene (also known as v-ets avian erythroblastosis virus *E26* oncogene homolog) is estimated to occur at a rate of 40–50% in prostate cancer. Early evidence suggests that ERG overexpression may be associated with disease progression, and the utilization of ERG levels as a biomarker for prostate cancer is being strongly considered. However, the evidence is incomplete because it relies on studies that primarily focused on men of European ancestry, giving little consideration to African–American men even though African–American men bear a greater disease burden in the form of significantly greater incidence and worse outcomes. In this perspective article we bring to light the issue that the potential use of ERG expression as a biomarker is yet to be solidly established and may have limited utility or varied applicability for African–American men as compared with European–American men.

Keywords

African–American; biomarker; ERG; prostate cancer

ERG is a member of the ETS transcription factor family and has been shown to be highly overexpressed in prostate cancer (PCa) with potential cancer-promoting functional consequences. Studies estimate that *ERG* gene rearrangement, which leads to *ERG* overexpression, occurs in PCa at an approximate frequency of 50% [1,2]. The rearrangement in general involves a somatic lesion, for example a genomic deletion, in chromosome region 21q22.2–3 that unites the androgen-responsive region from the *TMPRSS2* gene promoter and the *ERG* gene body [3–6]. This causes the androgen-dependent, upregulated expression

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and function of the ERG transcription factor, which underlies its malignant potential [7]. Multiple studies have examined the oncogenic potential of the gene expression program regulated by *TMPRSS2:ERG* fusion and overexpressed ERG transcription factor in PCa. They implicate ERG in regulating the increased expression of oncogenes, as well as genes that regulate developmental processes and genes that promote cancer invasion and migration [8–11]. Thus, the *TMPRSS2:ERG* fusion, and more specifically the resulting *ERG* gene overexpression, is mechanistically linked to promoting the expression of cancer phenotypes. However, it has also been demonstrated that the event is not sufficient for transformation of PCa in the absence of secondary molecular lesions [9,12].

The utilization of the *TMPRSS2:ERG* translocation or ERG expression as a bio-marker for prognosis, possibly added to PSA or other factors such as PTEN, is being strongly considered; and the development and implementation of ERG protein-level and mRNA expression-level assays, where high levels are shown to correlate with fusion gene status, are underway [13–16]. The reasoned application of these assays – to be utilized on patient prostate biopsy tissue or urine – is based on studies that identify an association for high ERG expression and high-grade prostatic intraepithelial neoplasia and high-grade cancer on biopsy [15,16]. Another promoted application is based on the assessment that the gene fusion almost always indicates cancer [17], here the detection of *TMPRSS2:ERG* fusion or high-levels of ERG expression would be used to diagnose the presence of PCa. These results, however, remain controversial in that they do not consider race or ethnicity, and the findings may not extend to African–American men, underscoring the need for more effort beyond the limited work that has been done to molecularly characterize PCa from African American men to overcome PCa disparities, reviewed in [18].

Existing data on ERG levels in PCa from African–Americans

Two studies report that *TMPRSS2:ERG* fusion events are less frequent in PCa specimens from African–American men compared with PCa from European–American men [19,20]. Adding to this, we recently reported results of high-throughput gene expression analysis of radical prostatectomy specimens from the biorepository at the Karmanos Cancer Institute in Detroit (MI, USA) demonstrating that the *ERG* is more highly expressed than any other genes in PCa from European–American men, although it is not highly expressed in PCa from African–American men [21]. Our significant observation comes from analysis of the largest diverse patient cohort reported on to date (PCa from 270 African–Americans and 369 European–Americans). Highly informative density plots of the expression data (Figure 1) unequivocally show two distinct subgroups of ERG expression in PCa from African–American and European–American populations. Furthermore, a strong statistically significant difference ($p < 0.001$) in the proportion of patients with high ERG expression level exists between African–American men (13.3%) and European–American men (38.5%). The measured differences were not artifacts of inconsistent sample treatment being that samples were carefully controlled, that is, all specimens were similarly processed within the same institute spanning years 1991–1996 and comprised 70% tumor cells according to pathologist review. Moreover, this is in agreement with another recent study reporting a low frequency for ERG protein expression among African–American men [20].

Association of ERG expression with clinical features

Previous studies identified significant associations for high ERG levels and poor outcomes [13,15,22–23]. Notably, these studies were lacking in that they did not adequately represent PCas from minority populations. Alogistic regression analysis testing the association between ERG transcript expression level class and categorized Gleason score (scores ranging from 3 to 10) found no association for African–American ($p = 0.36$; odds ratio for low relative to high class [OR]: 1.42; 95% CI: 0.57–3.03) or European–American men ($p = 0.40$; OR: 1.22; 95% CI: 0.77–1.95) (Table 1). However, by pooling the race-specific data sets into a single analysis data set to achieve greater numbers and more power, we found increased significance for a link between low ERG expression and high Gleason ($p = 0.08$; OR: 1.40; 95% CI: 0.96–2.05) (Table 2). Considering that a Gleason score 7(4+3) is a representative measure of more aggressive PCa [24], this result supports an alternate consideration for ERG as a biomarker such that high-level ERG expression may indicate a better prognosis irrespective of race. Further support for this notion comes from results of research of mixed populations that link high ERG protein levels and a less-aggressive phenotype [20].

The functionally relevant consequence of the *TMPRSS2:ERG* gene rearrangement, by either chromosomal translocation or deletion, is the upregulation of expression and accompanying oncogenic activation of the transcription factor that in turn regulates a number of genes implicated in PCa onset and progression [8–11,25]. Here we consider the possibility that alternative mechanisms independent of the *TMPRSS2:ERG* rearrangement regulate similar PCa gene expression profiles in African–American men. The prometa-static CXCR4, which is known to be regulated by androgen-induced, *TMPRSS2* promoter-driven ERG expression [25], serves as an example. Our previous study highlighted this gene as highly expressed in PCa specimens from African–American men, significantly higher than in European–American men [21]. It remains uncertain what mechanism alternative to the *TMPRSS2:ERG* fusion event may also upregulate CXCR4 expression in PCa from African–American men. In line with this, what also remains to be investigated is the frequency of gene fusions involving other members of the ETS transcription factor family and their regulation of gene expression in PCa from African–American men.

Future perspective

It is clear from genomic studies that the rate of *TMRSS2:ERG* fusions or ERG overexpression is at near 50% in PCa for men of European descent, but PCa from African–American men does not fit into this pattern of molecular subtyping. From studies of diverse populations, high-level ERG expression is overwhelmingly found in PCa from European American men and only a small subset of PCa from African–American men show high-level ERG expression. Furthermore, in contrast to earlier conclusions drawn largely from analysis of men of European descent, our study, which includes a diverse population, indicates that individuals with high ERG expression levels are more likely ($p = 0.08$) to have a less-aggressive cancer phenotype than individuals with low ERG expression. Altogether, the results indicate that the appropriate use of *ERG* as a biomarker requires further clarification;

and that if/ when an *ERG* test is ultimately be employed, it will need to consider the issue of patient race.

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Executive summary

- This perspective article discusses how efforts moving forward to utilize ERG expression or *TMPRSS2:ERG* translocation as a biomarker for prostate cancer detection or prognosis should more carefully consider how such tests may or may not apply to African American patients
- We are reporting that the percentage of increased ERG expression among African Americans is significantly lower than European American men and may have minimal benefit as a prostate cancer diagnostic marker among African American men..

Figure 1. Estimated density function and boxplots of the normalized log₂ ERG expression in prostate cancer stratified by race.

A cut-point was determined (ERG expression value where the pooled density between the two peaks is at its minimum = -0.61) to categorize the ERG expression values into low and high groups. A statistically significant difference ($p < 0.001$) exists for the proportion of patients with high ERG expression level in African-American (13.3%) and European-American (38.5%) populations.

AAM: African-Americans; EAM: European-Americans.

Table 1

Description of Gleason's score phenotype by race and ERG status using 7(4+3) to denote aggressive cancer.

Race	ERG class	GS 7(4+3) (n)	GS 7(3+4) (n)	High GS (%)	Odds ratio (95% CI)	p-value
AAM	High	11	25	30.6	1.42 (0.67–3.03)	0.36
AAM	Low	90	144	38.5		
EAM	High	38	104	26.8	1.22 (0.77–1.95)	0.40
EAM	Low	70	157	30.8		

The odds ratios listed compares the low ERG class relative to the high ERG class, stratified by race. The p-values test whether that odds ratios are equal to 1.

AAM: African-American men; EAM: European-American men; GS: Gleason's score.

Table 2

Description of Gleason's score phenotype by ERG status using 7(4+3) to denote aggressive cancer.

ERG class	GS 7(4+3) (n)	GS 7(3+4) (n)	High GS (%)	Odds ratio (95% CI)	p-value
High	49	129	27.5	1.40 (0.96-2.05)	0.08
Low	160	301	34.7		

The odds ratios listed compares the low ERG class relative to the high ERG class, stratified by race. The p-values tests whether that odds ratios are equal to 1.

GS: Gleason's score