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Research Paper

Integration of copy number and transcriptomics provides risk stratification in prostate cancer: A discovery and validation cohort study

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ABSTRACT

Background: Understanding the heterogeneous genotypes and phenotypes of prostate cancer is fundamental to improving the way we treat this disease. As yet, there are no validated descriptions of prostate cancer subgroups derived from integrated genomics linked with clinical outcome.
Methods: In a study of 482 tumour, benign and germline samples from 259 men with primary prostate cancer, we used integrative analysis of copy number alterations (CNA) and array transcriptomics to identify genomic loci that affect expression levels of mRNA in an expression quantitative trait loci (eQTL) approach, to stratify patients into subgroups that we then associated with future clinical behaviour, and compared with either CNA or transcriptomics alone.
Findings: We identified five separate patient subgroups with distinct genomic alterations and expression profiles based on 100 discriminating genes in our separate discovery and validation sets of 125 and 103 men. These subgroups were able to consistently predict biochemical relapse ($p = 0.0017$ and $p = 0.016$ respectively) and were further validated in a third cohort with long-term follow-up ($p = 0.027$). We show the relative contributions of gene expression and copy number data on phenotype, and demonstrate the improved power gained from integrative analyses. We confirm alterations in six genes previously associated with prostate cancer (*MAP3K7*, *MELK*, *RCBTB2*, *ELAC2*, *TPD52*, *ZBTB4*), and also identify 94 genes not previously linked to prostate cancer progression that would not have been detected using either transcript or copy number data alone. We confirm a number of previously published molecular changes associated with high risk disease, including *MYC* amplification, and *NKX3-1*, *RB1* and *PTEN* deletions, as well as over-expression of *PCA3* and *AMACR*, and loss of *MSMB* in tumour tissue. A subset of the 100 genes outperforms established clinical predictors of poor prognosis (PSA, Gleason score), as well as previously published gene signatures ($p = 0.0001$). We further show how our molecular profiles can be used for the early detection of aggressive cases in a clinical setting, and inform treatment decisions.

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Interpretation: For the first time in prostate cancer this study demonstrates the importance of integrated genomic analyses incorporating both benign and tumour tissue data in identifying molecular alterations leading to the generation of robust gene sets that are predictive of clinical outcome in independent patient cohorts.

1. Introduction

Disease stratification based on molecular signatures has aided the management of other epithelial cancers such as breast cancer (Curtis et al., 2012). In contrast, prostate cancer treatment decisions are still based almost exclusively on histological architecture (Gleason score) (Gleason, 1966; Gleason and Mellinger, 1974), prostate-specific antigen (PSA) levels (Catalona et al., 1994) and local disease state (TNM, WHO 2009), without attention to molecular characteristics. However, recent studies show that prostate cancer can be stratified according to molecular signatures (Glinsky et al., 2004; Varambally et al., 2005; Tomlins et al., 2007; Irshad et al., 2013; Taylor et al., 2010). Prostate cancer is the most non-cutaneous common cancer in males in the UK and USA (www.cancerresearchuk.org and www.cdc.gov) and genetic changes associated with aggressive disease, when present in early tumours, herald the onset of early biochemical relapse (Ramos-Montoya et al., 2014). Early treatment of primary prostate cancer is very effective, but it is still difficult to identify those patients who are likely to progress and to treat them appropriately.

Here we describe the comprehensive, integrated analysis of genomic and transcriptomic data from 351 tissue and blood samples from 156 British men, including 125 radical prostatectomy (RP) samples, 118 with matched benign tissue; 64 matched germline DNA; 19 castrate-resistant prostate cancer (CRPC) from channel transurethral resection of the prostate (chTURP) samples, 13 with matched germ-line DNA, and 12 independent samples with benign prostatic hyperplasia (BPH). We identify five distinct molecular profiles for primary prostate cancer that are predictive of biochemical relapse, based on the integrative analysis of transcript levels and somatic copy number alterations (CNAs). These findings hold when castrate-resistant prostate cancers are

Table 1
Summary of clinical characteristics of discovery (Cambridge) and validation (Stockholm) cohorts.

	Cambridge				Stockholm	
	Primary tumour — RP		CRPC — chTURP		Primary tumour — RP	
	n = 125	%	n = 19	%	n = 103	%
Age (years)						
Mean	60.9		72.4		63.9	
Range	41–73		59–93		54–75	
Pre-operative PSA (ng/ml)						
<4	3	2%	0		7	7%
4–10	87	70%	3	16%	60	58%
>10	34	27%	16	84%	28	27%
Unknown	1	1%	–		8	8%
Gleason Grade (RP)						
5	–		–		2	2%
6	18	14%	–		20	19%
7 (3 + 4)	76	61%			58	56%
7 (4 + 3)	21	17%	1	5%		
8	8	6%	2	11%	6	6%
9	2	2%	9	47%	9	9%
10	0	0%	2	11%	1	1%
Neuroendocrine	–		1	5%	–	
Small cell	–		1	5%	–	
Ungraded/unknown	–		1	5%	7	7%
Pathology stage						
pT2	38	30%	–		52	50%
pT3a	76	61%	–		28	27%
pT3b	9	7%	–		15	15%
pT4	2	2%	–			
Unknown					6	6%
Follow-up (months)						
Mean	37		–		78	
Range	2–67		–		2–122	
Biochemical relapse	21	17%	–		48	47%
% tumour cellularity						
Mean	52%		65%		tissue selected for ≥70%	
Range	20%–90%		20%–95%			
Positive surgical margins	30	24%	–		44	43%
Extra-capsular extension	87	70%	1	5%	43	42%
Metastases	1	1%	2	11%	4	4%
ERG status*						
2EDEL	8	6%	–		–	
2ESPLIT	12	10%	–		–	
EDEL	20	16%	–		–	
ESPLIT	17	14%	–		–	
N	64	51%	–		–	
Unknown	4	3%	–		–	

* According to Attard et al. (2008).