Published in final edited form as:

Curr Opin Genet Dev. 2009 February ; 19(1): 82–91. doi:10.1016/j.gde.2008.11.008.

Oncogenic Gene Fusions in Epithelial Carcinomas

John R. Prensner¹ and Arul M. Chinnaiyan^{1,2,3,4,5}

¹Michigan Center for Translational Pathology, University of Michigan Medical School, 1400 East Medical Center Drive, 5316 CCGC, Ann Arbor, MI 48109, USA

²Department of Pathology, University of Michigan Medical School, 1400 East Medical Center Drive, 5316 CCGC, Ann Arbor, MI 48109, USA

³Department of Urology, University of Michigan Medical School, 1400 East Medical Center Drive, 5316 CCGC, Ann Arbor, MI 48109, USA

⁴Howard Hughes Medical Institute, University of Michigan Medical School, 1400 East Medical Center Drive, 5316 CCGC, Ann Arbor, MI 48109, USA

⁵The Comprehensive Cancer Center, University of Michigan Medical School, 1400 East Medical Center Drive, 5316 CCGC, Ann Arbor, MI 48109, USA

Summary of Recent Advances

New discoveries regarding recurrent chromosomal aberrations in epithelial tumors have challenged the view that gene fusions play a minor role in these cancers. It is now known that recurrent fusions characterize significant subsets of prostate, breast, lung and renal-cell carcinomas, among others. This work has generated new insights into the molecular subtypes of tumors and highlighted important advances in bioinformatics, sequencing and microarray technology as tools for gene fusion discovery. Given the ubiquity of tyrosine kinases and transcription factors in gene fusions, further interest in the potential “druggability” of gene fusions with targeted therapeutics has also flourished. Nevertheless, the majority of chromosomal abnormalities in epithelial cancers remain uncharacterized, underscoring the limitations of our knowledge of carcinogenesis and the requirement for further research.

Introduction

The intrigue of chromosomal aberrations in human cancers dates back over 90 years, when early theories about the molecular and genetic origins of cancer were first being discussed. Since then, the genetic basis of cancer has been well established to include certain fundamental tumorigenic processes that accrue within cancer cells: most prominently, chromosomal aberrations, nucleotide substitutions, epigenetic changes and post-transcriptional dysregulation of gene expression [1].

Correspondence to: Arul M. Chinnaiyan, arul@umich.edu.

Disclosure: The University of Michigan has filed for a patent on the recurrent gene fusions in prostate cancer and A.M.C. is named as a co-inventor. The technology has been licensed to Gen-Probe Inc. to be developed as a molecular diagnostic. A.M.C. is a consultant to Gen-Probe.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

With more than 50,000 chromosomal alterations annotated in more than 11,500 publications [2], particular interest has focused on the tumorigenic potential of gene fusions. Historically these fusions have been mainly associated with hematological and mesenchymal malignancies. Despite over 440 known gene fusions in benign tumors and cancer [3], only ~15% of these and 10% of known recurrent breakpoint aberrations (RBAs) are found in epithelial tumors, of which only 35% have been characterized [4••]. By contrast, ~90% of known oncogenes are associated with somatic mutations [5]. The subsequent discovery of the TMPRSS2-Ets fusions in prostate cancer by our group [6••], and recurrent fusions lung cancer by others [7•,8•], has fueled investigations of the role of gene fusions in epithelial carcinomas. These findings suggest that numerous, undiscovered gene fusions may be lurking within the cancer genome. Here, we summarize the current state of gene fusions in epithelial cancers, highlighting the technologies that enabled these discoveries.

Historical Perspectives: Gene Fusions

Despite the current swell of interest in gene fusions, the seminal discovery in this field remains Nowell and Hungerford's identification, in 1960, of the BCR-ABL balanced translocation of the long arm of chromosome 22 to the short arm of chromosome 9 [9]. Resulting in constitutive activation of the Abl tyrosine kinase domains, the Bcr-Abl fusion protein is the driving force in chronic myelogenous leukemia (CML) [10,11]. By establishing a causal link between a specific chromosomal lesion and a specific malignancy, BCR-ABL also pioneered cancer therapy: the tyrosine kinase inhibitor, imatinib (Gleevec), was introduced as the first widely used targeted therapeutic [12].

Similar discoveries led to the characterization of causative fusions in a host of other hematological malignancies, including Burkitt's lymphoma, T Cell lymphomas and acute promyelocytic leukemia (AML), which harbors the retinoic acid-sensitive t(15;17) fusion of the transcription factor RAR α to PML [13]. Moreover, gene fusions play important roles in many soft tissue tumors, where over 40 known gene fusions have been characterized [14].

Gene Fusions in Epithelial Cancers

As with hematological malignancies, gene fusions in epithelial cancers can be broadly classified into two main groups: the tyrosine kinase (TK) fusions and the transcription factor (TF) fusions. Together, they account for 50% of the genes found in gene fusions (Table 1) [14]. While the two may functionally overlap *in vivo*—TKs can lead to TF phosphorylation, and TFs can influence the expression of TK genes—this distinction is a useful to envision the two major architectural frameworks for fusion proteins.

Tyrosine Kinase Fusions

With BCR-ABL as the presiding paradigm, chromosomal aberrations that activate TKs, especially receptor TKs (RTKs), have long been a focus in cancer biology. Upon extracellular ligand-binding, RTKs activate intracellular signaling pathways by dimerization of the receptor subunits and autophosphorylation of the tyrosine residues [15]. Once initiated, TK activity can lead to numerous cellular responses including increased proliferation, growth, gene expression, and suppression of apoptotic pathways, among others (Figure 1).

Given their widespread functionality in cellular growth and proliferation pathways, it is logical that TKs are prominent 3' partners in oncogenic gene fusions. The 5' partners for such fusions, however, comprise a more variegated group. This is perhaps most readily illustrated by the numerous RET and NTRK1 TK fusions of papillary thyroid cancer. These were linked to at least seventeen total 5' fusion partners that commonly confer dimerization capability through leucine zipper or coiled-coil domains (Table 1) [16]. Interestingly, fusions of RET and NTRK1,

which account for ~50% of papillary thyroid cancers, tend to segregate both from each other [17] and from mutations in the cytosolic kinase BRAF, which is mutated in as much as 40% of thyroid cancers [18].

Recently, several reports have described gene fusions in non-small-cell lung cancers (NSCLC) [7•]. With a prevalence of approximately 5% [7•,19], the EML4-ALK fusion, which has been linked to cellular transformation [20], increased cellular growth and decreased apoptosis [21], defines a subset of NSCLCs, segregating from mutations in EGFR and appearing more commonly in non-smokers [7•]. Rivoka et al. further used phosphoproteomics to conduct a large-scale survey of oncogenic kinases to identify novel gene fusions TFG-ALK and CD74-ROS1 in patients with NSCLC [8•]. In another context, ROS1 has also previously been implicated in rare GOPC-ROS1 fusions in glioblastoma [22].

Transcription Factor Fusions

The story of TF fusions in epithelial cancers spans both the rare oncologic curiosities and the ubiquitous oncologic diseases. As with TK fusions, TFs often form multiple fusion genes by involving many different 5' partners. The MiTF gene family of TFs, for example, define a subset of pediatric papillary renal-cell carcinomas with eight known 5' partners [23,24]. Interestingly, TFE3 and TFEB, two functionally-redundant MiTF factors implicated in these fusions [25,26], contribute to activation of MET RTK signaling, illustrating the interaction between kinases and TFs [27].

Unlike TKs, however, disruption of TF function by gene fusions can cause a dominant-negative effect on the cell. Indeed, dysregulation of TFE3 and TREB leads to a loss of MAD2B-controlled mitotic checkpoint regulation and disruption of tissue-specific development [28, 29]. Moreover, PAX8-PPAR γ fusions, found in ~50% of follicular thyroid cancer (FTC) [30] and the follicular variant of papillary thyroid cancer (FVPTC) [31], disrupt PPAR γ activation, leading to dysregulated cell-cycle transitions, decreased apoptosis, and cellular transformation [32,33]. Surprisingly, the PAX8-PPAR γ fusion, which is overexpressed in fusion-positive tumors, is associated with less aggressive tumor features and a better clinical outcome [34, 35].

Elsewhere, the clinical outcome associated with cancers harboring gene fusions is less sanguine. Rare but poorly differentiated pediatric carcinomas of midline structures, such as those in the head, neck and thorax, possess a distinctive t(15;19) BRD4-NUT fusion [36,37]. Likewise, in secretory breast cancer, a rare form of ductal carcinoma, the recurrent ETV6-NTRK3 fusion has been implicated in increased cellular viability and aberrant cell-cycle progression [38]. Moreover, mucoepidermoid carcinoma and pleiomorphic adenoma, the most common malignant and benign tumors of the salivary glands, respectively, both manifest prominent tumorigenic gene fusions [39-41].

Prostate Cancer

In 2005, our group described recurrent fusions between the Ets family TFs, ERG and ETV1, and the androgen-regulated transmembrane serine protease, TMPRSS2, in prostate cancer [6•]. Subsequently, multiple other 5' fusion partners have been described for ERG and ETV1, as well as other members of the Ets family (Table 2) [6•,42•]. The first major solid cancer to reveal such findings, roughly 60% of prostate cancers harbor a known fusion, of which 80-90% are TMPRSS2-ERG fusions [6•,43-45]. Because ERG and TMPRSS2 reside on the same region of chromosome 21, two mechanisms—an intrachromosomal deletion and an inversion—are implicated in their creation, though ultimately TMPRSS2 contributes only untranslated sequences to the final mRNA transcript [6•,46].

Following this discovery, TMPRSS2-Ets fusions have emerged as a major factor in prostate tumorigenesis, contributing to cellular invasiveness *in vitro* [42•,43,44]. While these fusions are common in pre-malignant prostate lesions [47-49], they are insufficient for the initiation of carcinogenesis in mouse models [46]. Given these data, we and others have posited that ERG cooperates with other early genomic alterations in prostate cancer, such as loss of the tumor suppressor PTEN, to induce an invasive phenotype [46].

Clinically, TMPRSS2-ERG fusions have also been correlated with a poorer prognosis and an increased risk of disease recurrence [50-54], although some discordant results have been found [55]. In this regard, analyzing the clinical impact of these fusions is complicated by the multifocal nature of prostate cancer [56], and recent reports show that the status of TMPRSS2-Ets fusions may be inconsistent in up to 70% of multifocal tumors [57,58]. Given the heterogeneous nature of many epithelial cancers, the detection and analysis of gene fusions in other major carcinomas may be impeded by similar complications of multifocality and clonal heterogeneity.

Advances in Gene Fusion Discovery

Our lab has developed several new methodologies for the identification and analysis of gene fusion candidates. In combination with mainstay wet-lab techniques such as fluorescence *in-situ* hybridization (FISH), our research incorporates computational and bioinformatic approaches to gene fusion biology, including cancer outlier profile analysis (COPA) [6••], the microarray compendium Oncomine [59•] and Molecular Concepts Mapping (MCM) analysis [60] (Box 1).

Box 1: Bioinformatic Gene Fusion Analysis

Discovery of fusions by gene expression microarrays often depends on the upregulation of the chimeric transcript or 3' functional end, which can be detected as an outlier. To analyze such data, our lab has developed three core bioinformatic tools.

COPA

Cancer Outlier Profile Analysis (COPA) highlights differential expression of genes screened with microarrays [6••]. By median-centering microarray data, COPA enhances the visibility of outlier genes, which may be candidate gene fusions.

Oncomine

With over 18,000 microarray experiments across 35 tumor types, Oncomine is a compendium used to corroborate expression data across multiple datasets, thereby decreasing the problem of false positives in any given microarray [59•]. Oncomine also visualizes expression data with features such as interactome analysis and Molecular Concepts analysis [59•].

MCM

The Molecular Concepts Map (MCM) nominates potential interactions between biological phenomena within cancer cells [60]. By combining data from Oncomine [59•] and the Connectivity Map [61••], MCM predicts mechanistic pathways, molecular characteristics, and interaction networks for candidate gene fusions.

Recently, other groups have developed new methods to analyze transcriptome and gene expression data. Lamb et al. have devised a bioinformatic tool to predict and nominate interactions between small molecule compounds and human tumors based upon microarray

expression analysis [61••]. This Connectivity Map offers a new paradigm for tumor-specific therapeutics.

To facilitate fusion discovery, Hahn et al. designed an algorithmic approach to query mRNA and expressed sequence tag (EST) databases for incongruous transcript sequences [62], and they nominated 20 putative recurrent fusion genes. While their approach has limitations—for example, they identified only 6 of 22 known Bcr-Abl fusion mRNAs—their findings offer intriguing insight into methods for identifying fusion genes.

Next Generation Sequencing

Recently, high-throughput “massively-parallel” sequencing platforms, including Roche/454, Applied Biosystems/SOLiD and Illumina/Solexa, have provided researchers with tantalizing new tools to study gene fusions. The depth of coverage offered by these platforms permits genome-wide and transcriptome-wide sequencing on a scale not previously feasible. Already, studies analyzing human transcriptomes [63•] and chromosomal breakpoints [64] demonstrate the utility of such modalities. The use of paired-end sequencing, which combines fragmented sample gDNA flanked with known reference sequences, is also a promising method for fusion discovery [65].

Next-generation sequencing platforms, however, also present challenges. Adaptor ligation steps may increase numbers of false positive fusion reads. Genome fragmentation into 30 to 300 bp segments (as compared to 900 bp for capillary sequencing) makes sequence re-assembly more challenging. The sheer volume of sequencing data makes bioinformatic and computational analysis difficult.

To this end, our lab has developed bioinformatic methods to categorize putative gene fusions and eliminate false positive reads. Combining longer ~300 bp reads from Roche/454 with 30-40 bp reads from Illumina/Solexa yields more specific results than either technology alone, allowing the identification of novel gene fusions in prostate cancer (Maher CA et al., in submission). As these technologies become more common, it is likely that many more gene fusions will be identified in this manner. Nevertheless, finding clinically significant, recurrent gene fusions remains challenging, and thus better paradigms may be required to combine these technologies with standard wet-lab techniques in fusion discovery.

Challenges and Future Directions

Significant obstacles still hinder genome and transcriptome analysis. Epithelial cancers, unlike many hematological cancers, frequently display highly aberrant karyotypes that are difficult to characterize cytogenetically. Clonal heterogeneity is common in epithelial cancers, with up to 80% of carcinomas harboring unrelated clones [66,67]. Finally, with the explosion of microarray data in the past decade, databases have been flooded with potential genomic, epigenetic, and transcriptomic aberrations in cancer. Isolating seminal events in tumorigenesis from such volumes is challenging, as false positives remain problematic.

Moving forward, it may be argued that the focus on fusions involving kinases and transcription factors is too narrow. It may be possible that “non-traditional” gene fusions involving protein-folding chaperones and cellular localization proteins, among others, are prominent in certain epithelial cancers. Such bias may partly resolve as computational tools, sequencing technologies and array-based assays become more powerful and precise. With the increased ability to interrogate the genome, putative gene fusions may be detected in a less biased manner. Clinically, this may result in the discovery of “non-traditional” gene fusions that—like BCR-ABL—serve as candidates for targeted therapy (Figure 2). Moreover, fusion transcripts may contribute to novel, non-invasive diagnostics if shed in the urine or detectable in blood serum.

Already, non-invasive clinical tests for TMPRSS2-ERG transcripts are under investigation [68].

Conversely, the clinical picture generated by fusions in epithelial cancers is unclear. Indeed, some fusions, such as PAX8-PPAR γ , counter-intuitively seem to characterize less aggressive disease. Yet, data in prostate cancer indicates that fusions may, in fact, define clinically important cancer subtypes. TMPRSS2-ERG fusions generated by intrachromosomal deletions, for example, tend to correspond with worse prognoses than those created by inversions [69]. Additionally, some fusion-based carcinomas are more prominent in pediatric populations, including renal-cell, thyroid, and aggressive midline carcinomas. As research progresses, such epidemiological and demographical data may allow for more specific applications of gene fusion-based targeted therapy.

Conclusions

Long considered a phenomenon of hematological and mesenchymal cancers, gene fusions are now emerging as an important component in epithelial carcinogenesis. With epithelial cancers accounting for 90% of all malignancies and 80% of cancer-related deaths [4•,14], new discoveries, particularly in breast, prostate, lung, and renal-cell carcinomas, show that recurrent gene fusions are widespread across epithelial cancers. Although much work is still needed, new technologies in sequencing, microarrays and bioinformatics hold promise for gene fusion discovery and facilitate the characterization of recurrent gene fusions in major epithelial cancers.

Acknowledgements

We thank Jill Granger for her critical reading of this manuscript. We thank the Howard Hughes Medical Institute, the Burroughs Wellcome Foundation, the Early Detection Research Network, the Prostate Cancer Foundation, the U.S. Department of Defense, the National Institutes of Health, and the Specialized Program in Research Excellence (SPORE) program. J.R. Prensner is a fellow in the University of Michigan Medical Scientist Training Program.

References and Recommended Reading

Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Hanahan D, Weinberg RA. The hallmarks of cancer. *Cell* 2000;100:57–70. [PubMed: 10647931]
2. Mitelman F, J B, Mertens F. Mitelman Database of Chromosome Aberrations in Cancer [online]. 2008 Edited by
3. Heim S, Mitelman F. Molecular screening for new fusion genes in cancer. *Nat Genet* 2008;40:685–686. [PubMed: 18509307]
- 4. Mitelman F, Mertens F, Johansson B. Prevalence estimates of recurrent balanced cytogenetic aberrations and gene fusions in unselected patients with neoplastic disorders. *Genes Chromosomes Cancer* 2005;43:350–366.366 [PubMed: 15880352]. The most exhaustive study of chromosomal aberrations across cancer types The authors catalogue and analyze an immense amount of data to distill the most accurate account of chromosomal abnormalities in cancer available.
5. Futreal PA, Coin L, Marshall M, Down T, Hubbard T, Wooster R, Rahman N, Stratton MR. A census of human cancer genes. *Nat Rev Cancer* 2004;4:177–183. [PubMed: 14993899]
- 6. Tomlins SA, Rhodes DR, Perner S, Dhanasekaran SM, Mehra R, Sun XW, Varambally S, Cao X, Tchinda J, Kuefer R, et al. Recurrent fusion of TMPRSS2 and ETS transcription factor genes in prostate cancer. *Science* 2005;310:644–648.648 [PubMed: 16254181]. Using novel bioinformatic techniques, the authors describe the first example of a highly prevalent oncogenic gene fusion in a

highly prevalent and lethal epithelial cancer. The authors use gene expression arrays to analyze outliers and identify gene fusions. This paper reinvigorated research efforts to find fusion events in carcinomas.

- 7. Soda M, Choi YL, Enomoto M, Takada S, Yamashita Y, Ishikawa S, Fujiwara S, Watanabe H, Kurashina K, Hatanaka H, et al. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. *Nature* 2007;448:561–566. [PubMed: 17625570]. This paper describes the first recurrent gene fusion in non-small-cell lung cancer. It identifies a transforming tyrosine kinase fusion that may serve as a promising candidate for targeted therapy.
- 8. Rikova K, Guo A, Zeng Q, Possemato A, Yu J, Haack H, Nardone J, Lee K, Reeves C, Li Y, et al. Global survey of phosphotyrosine signaling identifies oncogenic kinases in lung cancer. *Cell* 2007;131:1190–1203. [PubMed: 18083107]. Employing a phosphoproteomic approach, the authors study phosphotyrosine signaling in over 150 non-small-cell lung cancers and 40 similar cell lines. The comprehensive findings give an informative picture of tyrosine kinase signaling in lung cancer, including both point mutations and novel gene fusions.
9. Nowell PC, Hungerford DA. Chromosome studies on normal and leukemic human leukocytes. *J Natl Cancer Inst* 1960;25:85–109. [PubMed: 14427847]
10. Lugo TG, Pendergast AM, Muller AJ, Witte ON. Tyrosine kinase activity and transformation potency of bcr-abl oncogene products. *Science* 1990;247:1079–1082. [PubMed: 2408149]
11. Daley GQ, Van Etten RA, Baltimore D. Induction of chronic myelogenous leukemia in mice by the P210bcr/abl gene of the Philadelphia chromosome. *Science* 1990;247:824–830. [PubMed: 2406902]
12. Druker BJ, Talpaz M, Resta DJ, Peng B, Buchdunger E, Ford JM, Lydon NB, Kantarjian H, Capdeville R, Ohno-Jones S, et al. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. *N Engl J Med* 2001;344:1031–1037. [PubMed: 11287972]
13. Goddard AD, Borrow J, Freemont PS, Solomon E. Characterization of a zinc finger gene disrupted by the t(15;17) in acute promyelocytic leukemia. *Science* 1991;254:1371–1374. [PubMed: 1720570]
14. Mitelman F, Johansson B, Mertens F. Fusion genes and rearranged genes as a linear function of chromosome aberrations in cancer. *Nat Genet* 2004;36:331–334. [PubMed: 15054488]
15. Blume-Jensen P, Hunter T. Oncogenic kinase signalling. *Nature* 2001;411:355–365. [PubMed: 11357143]
16. Nikiforov YE. Thyroid carcinoma: molecular pathways and therapeutic targets. *Mod Pathol* 2008;21 (Suppl 2):S37–43. [PubMed: 18437172]
17. Bongarzone I, Vigneri P, Mariani L, Collini P, Pilotti S, Pierotti MA. RET/NTRK1 rearrangements in thyroid gland tumors of the papillary carcinoma family: correlation with clinicopathological features. *Clin Cancer Res* 1998;4:223–228. [PubMed: 9516975]
18. Soares P, Trovisco V, Rocha AS, Lima J, Castro P, Preto A, Maximo V, Botelho T, Seruca R, Sobrinho-Simoes M. BRAF mutations and RET/PTC rearrangements are alternative events in the etiopathogenesis of PTC. *Oncogene* 2003;22:4578–4580. [PubMed: 12881714]
19. Perner S, Wagner PL, Demichelis F, Mehra R, Lafargue CJ, Moss BJ, Arbogast S, Soltermann A, Weder W, Giordano TJ, et al. EML4-ALK fusion lung cancer: a rare acquired event. *Neoplasia* 2008;10:298–302. [PubMed: 18320074]
20. Choi YL, Takeuchi K, Soda M, Inamura K, Togashi Y, Hatano S, Enomoto M, Hamada T, Haruta H, Watanabe H, et al. Identification of novel isoforms of the EML4-ALK transforming gene in non-small cell lung cancer. *Cancer Res* 2008;68:4971–4976. [PubMed: 18593892]
21. Koivunen JP, Mermel C, Zejnullahu K, Murphy C, Lifshits E, Holmes AJ, Choi HG, Kim J, Chiang D, Thomas R, et al. EML4-ALK fusion gene and efficacy of an ALK kinase inhibitor in lung cancer. *Clin Cancer Res* 2008;14:4275–4283. [PubMed: 18594010]
22. Charest A, Lane K, McMahon K, Park J, Preisinger E, Conroy H, Housman D. Fusion of FIG to the receptor tyrosine kinase ROS in a glioblastoma with an interstitial del(6)(q21q21). *Genes Chromosomes Cancer* 2003;37:58–71. [PubMed: 12661006]
23. Medendorp K, van Groningen JJ, Schepens M, Vreede L, Thijssen J, Schoenmakers EF, van den Hurk WH, Geurts van Kessel A, Kuiper RP. Molecular mechanisms underlying the MiT translocation subgroup of renal cell carcinomas. *Cytogenet Genome Res* 2007;118:157–165. [PubMed: 18000366]
24. Argani P, Ladanyi M. Translocation carcinomas of the kidney. *Clin Lab Med* 2005;25:363–378. [PubMed: 15848741]

25. Huan C, Kelly ML, Steele R, Shapira I, Gottesman SR, Roman CA. Transcription factors TFE3 and TFEB are critical for CD40 ligand expression and thymus-dependent humoral immunity. *Nat Immunol* 2006;7:1082–1091. [PubMed: 16936731]
26. Steingrimsdottir E, Tessarollo L, Pathak B, Hou L, Arnheiter H, Copeland NG, Jenkins NA. Mitf and Tfe3, two members of the Mitf-Tfe family of bHLH-Zip transcription factors, have important but functionally redundant roles in osteoclast development. *Proc Natl Acad Sci U S A* 2002;99:4477–4482. [PubMed: 11930005]
27. Tsuda M, Davis IJ, Argani P, Shukla N, McGill GG, Nagai M, Saito T, Lae M, Fisher DE, Ladanyi M. TFE3 fusions activate MET signaling by transcriptional up-regulation, defining another class of tumors as candidates for therapeutic MET inhibition. *Cancer Res* 2007;67:919–929. [PubMed: 17283122]
28. Mathur M, Samuels HH. Role of PSF-TFE3 oncoprotein in the development of papillary renal cell carcinomas. *Oncogene* 2007;26:277–283. [PubMed: 16832349]
29. Weterman MA, van Groningen JJ, Tertoolen L, van Kessel AG. Impairment of MAD2B-PRCC interaction in mitotic checkpoint defective t(X;1)-positive renal cell carcinomas. *Proc Natl Acad Sci U S A* 2001;98:13808–13813. [PubMed: 11717438]
30. Kroll TG, Sarraf P, Pecciarini L, Chen CJ, Mueller E, Spiegelman BM, Fletcher JA. PAX8-PPARgamma1 fusion oncogene in human thyroid carcinoma [corrected]. *Science* 2000;289:1357–1360. [PubMed: 10958784]
31. Castro P, Rebocho AP, Soares RJ, Magalhaes J, Roque L, Trovisco V, Vieira de Castro I, Cardoso-de-Oliveira M, Fonseca E, Soares P, et al. PAX8-PPARgamma rearrangement is frequently detected in the follicular variant of papillary thyroid carcinoma. *J Clin Endocrinol Metab* 2006;91:213–220. [PubMed: 16219715]
32. Gregory Powell J, Wang X, Allard BL, Sahin M, Wang XL, Hay ID, Hiddinga HJ, Deshpande SS, Kroll TG, Grebe SK, et al. The PAX8/PPARgamma fusion oncoprotein transforms immortalized human thyrocytes through a mechanism probably involving wild-type PPARgamma inhibition. *Oncogene* 2004;23:3634–3641. [PubMed: 15077183]
33. Au AY, McBride C, Wilhelm KG Jr, Koenig RJ, Speller B, Cheung L, Messina M, Wentworth J, Tasevski V, Learoyd D, et al. PAX8-peroxisome proliferator-activated receptor gamma (PPARgamma) disrupts normal PAX8 or PPARgamma transcriptional function and stimulates follicular thyroid cell growth. *Endocrinology* 2006;147:367–376. [PubMed: 16179407]
34. Sahin M, Allard BL, Yates M, Powell JG, Wang XL, Hay ID, Zhao Y, Goellner JR, Sebo TJ, Grebe SK, et al. PPARgamma staining as a surrogate for PAX8/PPARgamma fusion oncogene expression in follicular neoplasms: clinicopathological correlation and histopathological diagnostic value. *J Clin Endocrinol Metab* 2005;90:463–468. [PubMed: 15483076]
35. Marques AR, Espadinha C, Frias MJ, Roque L, Catarino AL, Sobrinho LG, Leite V. Underexpression of peroxisome proliferator-activated receptor (PPAR)gamma in PAX8/PPARgamma-negative thyroid tumours. *Br J Cancer* 2004;91:732–738. [PubMed: 15238980]
36. French CA, Miyoshi I, Kubonishi I, Grier HE, Perez-Atayde AR, Fletcher JA. BRD4-NUT fusion oncogene: a novel mechanism in aggressive carcinoma. *Cancer Res* 2003;63:304–307. [PubMed: 12543779]
37. French CA, Miyoshi I, Aster JC, Kubonishi I, Kroll TG, Dal Cin P, Vargas SO, Perez-Atayde AR, Fletcher JA. BRD4 bromodomain gene rearrangement in aggressive carcinoma with translocation t(15;19). *Am J Pathol* 2001;159:1987–1992. [PubMed: 11733348]
38. Tognon C, Knezevich SR, Huntsman D, Roskelley CD, Melnyk N, Mathers JA, Becker L, Carneiro F, MacPherson N, Horsman D, et al. Expression of the ETV6-NTRK3 gene fusion as a primary event in human secretory breast carcinoma. *Cancer Cell* 2002;2:367–376. [PubMed: 12450792]
39. Tonon G, Modi S, Wu L, Kubo A, Coxon AB, Komiyama T, O'Neil K, Stover K, El-Naggar A, Griffin JD, et al. t(11;19)(q21;p13) translocation in mucoepidermoid carcinoma creates a novel fusion product that disrupts a Notch signaling pathway. *Nat Genet* 2003;33:208–213. [PubMed: 12539049]
40. Stenman G. Fusion oncogenes and tumor type specificity--insights from salivary gland tumors. *Semin Cancer Biol* 2005;15:224–235. [PubMed: 15826837]

41. Kas K, Voz ML, Roijer E, Astrom AK, Meyen E, Stenman G, Van de Ven WJ. Promoter swapping between the genes for a novel zinc finger protein and beta-catenin in pleiomorphic adenomas with t (3;8)(p21;q12) translocations. *Nat Genet* 1997;15:170–174. [PubMed: 9020842]
42. Tomlins SA, Laxman B, Dhanasekaran SM, Helgeson BE, Cao X, Morris DS, Menon A, Jing X, Cao Q, Han B, et al. Distinct classes of chromosomal rearrangements create oncogenic ETS gene fusions in prostate cancer. *Nature* 2007;448:595–599. [PubMed: 17671502]. By characterizing multiple types of gene fusions in prostate cancer, the authors show that gene fusions can describe specific molecular subtypes, like those in hematological cancers, in epithelial cancers.
43. Perner S, Demichelis F, Beroukhi R, Schmidt FH, Mosquera JM, Setlur S, Tchinda J, Tomlins SA, Hofer MD, Pienta KG, et al. TMPRSS2:ERG fusion-associated deletions provide insight into the heterogeneity of prostate cancer. *Cancer Res* 2006;66:8337–8341. [PubMed: 16951139]
44. Soller MJ, Isaksson M, Elfving P, Soller W, Lundgren R, Panagopoulos I. Confirmation of the high frequency of the TMPRSS2/ERG fusion gene in prostate cancer. *Genes Chromosomes Cancer* 2006;45:717–719. [PubMed: 16575875]
45. Yoshimoto M, Joshua AM, Chilton-Macneill S, Bayani J, Selvarajah S, Evans AJ, Zielenska M, Squire JA. Three-color FISH analysis of TMPRSS2/ERG fusions in prostate cancer indicates that genomic microdeletion of chromosome 21 is associated with rearrangement. *Neoplasia* 2006;8:465–469. [PubMed: 16820092]
46. Tomlins SA, Laxman B, Varambally S, Cao X, Yu J, Helgeson BE, Cao Q, Prensner JR, Rubin MA, Shah RB, et al. Role of the TMPRSS2-ERG gene fusion in prostate cancer. *Neoplasia* 2008;10:177–188. [PubMed: 18283340]
47. Perner S, Mosquera JM, Demichelis F, Hofer MD, Paris PL, Simko J, Collins C, Bismar TA, Chinnaiyan AM, De Marzo AM, et al. TMPRSS2-ERG fusion prostate cancer: an early molecular event associated with invasion. *Am J Surg Pathol* 2007;31:882–888. [PubMed: 17527075]
48. Cerveira N, Ribeiro FR, Peixoto A, Costa V, Henrique R, Jeronimo C, Teixeira MR. TMPRSS2-ERG gene fusion causing ERG overexpression precedes chromosome copy number changes in prostate carcinomas and paired HGPIN lesions. *Neoplasia* 2006;8:826–832. [PubMed: 17032499]
49. Mosquera JM, Perner S, Genega EM, Sanda M, Hofer MD, Mertz KD, Paris PL, Simko J, Bismar TA, Ayala G, et al. Characterization of TMPRSS2-ERG fusion high-grade prostatic intraepithelial neoplasia and potential clinical implications. *Clin Cancer Res* 2008;14:3380–3385. [PubMed: 18519767]
50. Rajput AB, Miller MA, De Luca A, Boyd N, Leung S, Hurtado-Coll A, Fazli L, Jones EC, Palmer JB, Gleave ME, et al. Frequency of the TMPRSS2:ERG gene fusion is increased in moderate to poorly differentiated prostate cancers. *J Clin Pathol* 2007;60:1238–1243. [PubMed: 17259299]
51. Yoshimoto M, Joshua AM, Cunha IW, Coudry RA, Fonseca FP, Ludkovski O, Zielenska M, Soares FA, Squire JA. Absence of TMPRSS2:ERG fusions and PTEN losses in prostate cancer is associated with a favorable outcome. *Mod Pathol*. 2008
52. Setlur SR, Mertz KD, Hoshida Y, Demichelis F, Lupien M, Perner S, Sboner A, Pawitan Y, Andren O, Johnson LA, et al. Estrogen-dependent signaling in a molecularly distinct subclass of aggressive prostate cancer. *J Natl Cancer Inst* 2008;100:815–825. [PubMed: 18505969]
53. Demichelis F, Fall K, Perner S, Andren O, Schmidt F, Setlur SR, Hoshida Y, Mosquera JM, Pawitan Y, Lee C, et al. TMPRSS2:ERG gene fusion associated with lethal prostate cancer in a watchful waiting cohort. *Oncogene* 2007;26:4596–4599. [PubMed: 17237811]
54. Attard G, Clark J, Ambrosini L, Fisher G, Kovacs G, Flohr P, Berney D, Foster CS, Fletcher A, Gerald WL, et al. Duplication of the fusion of TMPRSS2 to ERG sequences identifies fatal human prostate cancer. *Oncogene*. 2007
55. Saramaki OR, Harjula AE, Martikainen PM, Vessella RL, Tammela TL, Visakorpi T. TMPRSS2:ERG fusion identifies a subgroup of prostate cancers with a favorable prognosis. *Clin Cancer Res* 2008;14:3395–3400. [PubMed: 18519769]
56. Arora R, Koch MO, Eble JN, Ulbright TM, Li L, Cheng L. Heterogeneity of Gleason grade in multifocal adenocarcinoma of the prostate. *Cancer* 2004;100:2362–2366. [PubMed: 15160339]
57. Furusato B, Gao CL, Ravindranath L, Chen Y, Cullen J, McLeod DG, Dobi A, Srivastava S, Petrovics G, Sesterhenn IA. Mapping of TMPRSS2-ERG fusions in the context of multi-focal prostate cancer. *Mod Pathol*. 2007

58. Mehra R, Han B, Tomlins SA, Wang L, Menon A, Wasco MJ, Shen R, Montie JE, Chinnaiyan AM, Shah RB. Heterogeneity of TMPRSS2 gene rearrangements in multifocal prostate adenocarcinoma: molecular evidence for an independent group of diseases. *Cancer Res* 2007;67:7991–7995. [PubMed: 17804708]
- 59. Rhodes DR, Kalyana-Sundaram S, Mahavisno V, Varambally R, Yu J, Briggs BB, Barrette TR, Anstet MJ, Kincead-Beal C, Kulkarni P, et al. Oncomine 3.0: genes, pathways, and networks in a collection of 18,000 cancer gene expression profiles. *Neoplasia* 2007;9:166–180.180 [PubMed: 17356713]. An update of the original Oncomine paper, the authors illustrate the utility of bioinformatics in organizing and analyzing microarray data By grouping microarray datasets into a compendium, the authors developed a bioinformatic tool to interrogate the underlying molecular events in carcinogenesis as well as visualizing molecular interactions Since its launch, Oncomine has become a standard bioinformatic tool.
60. Rhodes DR, Kalyana-Sundaram S, Tomlins SA, Mahavisno V, Kasper N, Varambally R, Barrette TR, Ghosh D, Varambally S, Chinnaiyan AM. Molecular concepts analysis links tumors, pathways, mechanisms, and drugs. *Neoplasia* 2007;9:443–454. [PubMed: 17534450]
- 61. Lamb J, Crawford ED, Peck D, Modell JW, Blat IC, Wrobel MJ, Lerner J, Brunet JP, Subramanian A, Ross KN, et al. The Connectivity Map: using gene-expression signatures to connect small molecules, genes, and disease. *Science* 2006;313:1929–1935.1935 [PubMed: 17008526]. Using small molecule libraries and gene expression data, the authors created a bioinformatic tool to use gene expression profiles to match the effects and applicability of specific small molecule inhibitors on specific tumors By coupling therapeutics with tumor gene expression profiles, this paper provides a powerful model for nominating future cancer therapies.
62. Hahn Y, Bera TK, Gehlhaus K, Kirsch IR, Pastan IH, Lee B. Finding fusion genes resulting from chromosome rearrangement by analyzing the expressed sequence databases. *Proc Natl Acad Sci U S A* 2004;101:13257–13261. [PubMed: 15326299]
- 63. Sultan M, Schulz MH, Richard H, Magen A, Klingenhoff A, Scherf M, Seifert M, Borodina T, Soldatov A, Parkhomchuk D, et al. A global view of gene activity and alternative splicing by deep sequencing of the human transcriptome. *Science* 2008;321:956–960.960 [PubMed: 18599741]. Using next-generation sequencing platforms, the authors survey the human transcriptome in human embryonic kidney cells and B cells As the most comprehensive description of the human transcriptome, they find large numbers of transcript-level events not previously reported This study demonstrates the potential of next-generation sequencing in characterizing the transcriptomes of human cancers.
64. Chen W, Kalscheuer V, Tzschach A, Menzel C, Ullmann R, Schulz MH, Erdogan F, Li N, Kijas Z, Arkesteijn G, et al. Mapping translocation breakpoints by next-generation sequencing. *Genome Res* 2008;18:1143–1149. [PubMed: 18326688]
65. Bashir A, Volik S, Collins C, Bafna V, Raphael BJ. Evaluation of paired-end sequencing strategies for detection of genome rearrangements in cancer. *PLoS Comput Biol* 2008;4:e1000051. [PubMed: 18404202]
66. Gasparini P, Sozzi G, Pierotti MA. The role of chromosomal alterations in human cancer development. *J Cell Biochem* 2007;102:320–331. [PubMed: 17722107]
67. Gorunova L, Hoglund M, Andren-Sandberg A, Dawiskiba S, Jin Y, Mitelman F, Johansson B. Cytogenetic analysis of pancreatic carcinomas: intratumor heterogeneity and nonrandom pattern of chromosome aberrations. *Genes Chromosomes Cancer* 1998;23:81–99. [PubMed: 9739011]
68. Hessels D, Smit FP, Verhaegh GW, Witjes JA, Cornel EB, Schalken JA. Detection of TMPRSS2-ERG fusion transcripts and prostate cancer antigen 3 in urinary sediments may improve diagnosis of prostate cancer. *Clin Cancer Res* 2007;13:5103–5108. [PubMed: 17785564]
69. Attard G, Clark J, Ambrosine L, Fisher G, Kovacs G, Flohr P, Berney D, Foster CS, Fletcher A, Gerald WL, et al. Duplication of the fusion of TMPRSS2 to ERG sequences identifies fatal human prostate cancer. *Oncogene* 2008;27:253–263. [PubMed: 17637754]

Figure 1. Biochemical Pathways in Gene Fusions

Biochemical effects of gene fusions cluster around tyrosine kinase (TK) signaling pathways, which alter the activity of intracellular proteins, and transcription factor (TF) activity, which control gene expression at the DNA level. Here we outline the examples of the Ras and PI-3K pathways, which are commonly involved downstream of TK activation and are frequently implicated in the oncogenic effects of gene fusions. PI-3K works via increased activity of the master regulator Akt, which controls many cellular processes including the nuclear TF NFκB. Likewise, the Ras-Raf-Mek-Erk pathway promotes activation of TFs, including Elk-1, which is a target of Erk. These signaling pathways and gene expression signatures result in the phenotypic qualities, such as invasiveness and increased proliferation, observed in cancers.

Figure 2. Gene Fusion Discovery and Targeted Therapy

Bioinformatic, sequencing and microarray methods are powerful tools for identifying potential gene fusions in epithelial cancers. By determining the genomic and transcriptomic events in human cancers, clinical management of the disease may be impacted, and gene fusions, such as the *TMPRSS2-Ets* fusions in prostate cancer, may serve as prominent therapeutic targets. If targeted therapeutics are successfully developed for critical oncogenes, clinical management of cancer may one day be determined based upon genetic evaluation of patient tumors.

Table 1**Gene Fusions in Epithelial Cancers**

Gene fusions characterize subsets of several different epithelial carcinomas, including thyroid, prostate, lung, and breast cancer. Gene fusions are broadly classified into two groups: those that contain tyrosine kinases (TKs), which activate intracellular signaling pathways, and those that contain transcription factors (TFs), which control cellular gene expression. Together, TKs and TFs account for 50% of the genes involved in gene fusions. Though most fusions occur at low prevalence rates, some, such as TMRSS2-ERG in prostate cancer and RET rearrangements in papillary thyroid cancer, among others, are predominant genomic lesions in the disease. Cytogenetically, fusions can be formed by inversions (inv) on a single chromosome, translocations between two genomic loci (t), or intrachromosomal deletions (del). With the exception of pleomorphic adenomas, this table includes fusions confirmed in human cancer samples. Fusions observed only in tumor-derived cell lines are not included.

Gene Fusions in Carcinomas				
Tyrosine Kinase Fusions				
Papillary Thyroid Carcinoma*	5' Partner	3' Partner	Prevalence	References
inv(10)(q11.2;q21)	HRH4	RET	30-80%	Grieco et al. Cell 1990
t(10;17)(q11.2;q23)	Ria	RET	5%	Bongarzone et al. Mol Cell Biol 1993
inv(10)(q11;q22)	NCOA4	RET	15-70%	Bongarzone et al. Cancer Res 1994; Santoro et al. Oncogene 1994
inv(10)(q11;q22)	RFG	RET	<1%	Bongarzone et al. Cancer Res 1994; Santoro et al. Oncogene 1994
t(10;14)(q11.2;q32)	GOLGA5	RET	<1%	Klugbauer et al. Cancer Res 1998
t(7;10)(q32-34;q11.2)	TRIM24	RET	<1%	Klugbauer and Rabes. Oncogene 1999
t(1;10)(p13;q11.2)	TRIM33	RET	<1%	Klugbauer and Rabes. Oncogene 1999
t(10;12)(q11.2;p13.3)	ERC1	RET	<1%	Nakata et al. Genes, Chromosomes Cancer 1999; Liu et al. Thyroid 2005
t(10;14)(q11.2;q22.1)	KTN1	RET	<1%	Salassidis 2000
t(10;18)(q11.2;q21-22)	RFG9	RET	<1%	Klugbauer et al. Cancer Res 2000
t(8;10)(p21-22;q11.2)	PCM1	RET	<1%	Corvi et al. Oncogene 2000
t(6;10)(p21;q11.2)	TRIM27	RET	<1%	Saenko et al. Mutat Res 2003
t(10;14)(q32.12;q11.2)	GOLGA5	RET	<1%	Rabes et al. Clin Cancer Res 2000
t(8;10)(p11.21;q11.2)	HOOK3	RET	<1%	Ciampi et al. Endocr Relat Cancer 2007
inv(1)(q21;q22)	TPM3	NTRK1	In total, 7-12% of	Greco et al. Oncogene 1992

Gene Fusions in Carcinomas				
Tyrosine Kinase Fusions				
Papillary Thyroid Carcinoma *	5' Partner	3' Partner	Prevalence	References
inv(1)(q21;q25)	TPM3	TPR	papillary thyroid cancers	Greco et al. Oncogene 1992
inv(1)(q21;q25)	TPR	NTRK1		Greco et al. Genes, Chromosomes Cancer 1997
t(1;3)(q21-22;q11)	TFG	NTRK1		Greco et al. Mol Cell Biol 1995
t(7;7)(q21-22;q34)	AKAP9	BRAF	<1%	Ciampi et al. J Clin Invest 2005
Secretory Breast Cancer				
t(12;15)(p13;q25)	ETV6	NTRK3	>90%	Tognon et al. Cancer Cell 2002
Non-small cell Lung Cancer				
inv(2)(p23;p21) or t(2;2)(p23;p21)	EML4	ALK	2.7 - 6.7%	Soda et al. Nature 2007; Perner et al. Neoplasia 2008
t(6;13)(q22;)	CD74	ROS1	<1%	Rikova et al. Cell 2007
t(2;3)(p23;q12.2)	TFG	ALK	<1%	Rikova et al. Cell 2007
Glioblastoma				
del(6)(q21;q21)	GOPC	ROS1	not reported	Charest et al. PNAS 2003
Transcription Factor Fusions				
Prostate Cancer	5' Partner	3' Partner	Prevalence	References
inv(21)(q22.2;q22.3) or del(21)(q22.2;q22.3)	TMPRSS2	ERG	~50%	Tomlins et al. Science 2005
t(1;21)(q32;q22.2)	SLC45A3	ERG	<1%	Han et al. Cancer Res 2008
t(7;21)(p21.2;q22.3)	TMPRSS2	ETV1	5-10%	Tomlins et al. Science 2005
t(7;22)(p21.2;q11.23)	HERV_K_22q11.2.3	ETV1	<1%	Tomlins et al. Nature 2007
t(7;15)(p21.3;q21)	C15orf21	ETV1	1%	Tomlins et al. Nature 2007
t(7;7)(p21.2;p15)	HNRPA2B1	ETV1	1%	Tomlins et al. Nature 2007
t(1;7)(q32;p21.2)	SLC45A3	ETV1	2%	Tomlins et al. Nature 2007
t(2;7)(q36.1;p21.2)	ACSL3	ETV1	<1%	Attard et al. Br J Cancer 2008
t(7;14)(p21.2;q13.3-q21.1)	Not Known	ETV1	<1%	Attard et al. Br J Cancer 2008
t(7;17)(p21.2;p13.1)	FLJ35294	ETV1	<1%	Han et al. Cancer Res 2008
t(17;21)(q21;q22.3)	TMPRSS2	ETV4	<5%	Tomlins et al. Cancer Res 2008

Gene Fusions in Carcinomas				
Tyrosine Kinase Fusions				
Papillary Thyroid Carcinoma [*]	5' Partner	3' Partner	Prevalence	References
t(17;19)(q21;q13)	KLK2	ETV4	<1%	Hermans et al. Cancer Res 2008
inv(17;17)(q22;q25)	CANT1	ETV4	<1%	Hermans et al. Cancer Res 2008
t(17;17)(q21;q21)	DDX5	ETV4	<1%	Han et al. Cancer Research 2008
t(3;21)(q27;q22.3)	TMPRSS2	ETV5	<5%	Helgeson et al. Cancer Res 2008
t(1;3)(q32;q27)	SLC45A3	ETV5	<1%	Helgeson et al. Cancer Res 2008
Renal-cell Carcinoma				
t(X;1)(p11;q21)	PRCC	TFE3	In total, 10-15% of all renal tumors	Weterman et al. PNAS 1996; Sidhar et al. Hum Mol Genet 1996
t(X;17)(p11;q25)	ASPSCR1	TFE3		Argani Am J Pathol 2001
t(6;11)(p21.1;q13)	Alpha	TFEB		Davis et al. PNAS 2003
t(X;1)(p11;p34)	SFPQ	TFE3		Clark et al. Oncogene 1997
inv(X)(p11;q12)	NonO	TFE3		Clark et al. Oncogene 1997
t(X;17)(p11.2;q23)	CLTC	TFE3		Argani et al. Oncogene 2003
t(X;17)(p11.2;q25.3)	RCC17	TFE3		Heimann et al. Cancer Res 2001
Salivary Gland Tumors				
Pleiomorphic				
Adenoma				
t(3;8)(p21;q12)	CTNNB1	PLAG1	In total, ~40% of all pleiomorphic adenomas	Kas et al. Nat Genet 1997
t(5;8)(p13;q12)	LIFR	PLAG1		Voz et al. Oncogene 1998
t(8;8)(q12;q11.2)	TCEA1	PLAG1		Atrom et al. Cancer Res 1999
t(8;8)(q12;q11.2)	CHCHD7	PLAG1		Asp et al. Genes Chromosomes Cancer 2006
t(3;13)(p14.2;q13-15)	HMGA2	FHIT	<1%	Geurts et al. Cancer Res 1997
t(9;12)(p12-22;q13-15) or ins(9;12)	HMGA2	NFIB	8-12%	Geurts et al. Oncogene 1998
Mucoepidermoid Carcinoma				
t(11;19)(q21-22;p13)	CRC1	MAML2	30 - 75%	Nordkvist et al. Cancer Genet Cytogen 1994; Tonon et al. Nat Genet 2003

Gene Fusions in Carcinomas				
Tyrosine Kinase Fusions				
Papillary Thyroid Carcinoma *	5' Partner	3' Partner	Prevalence	References
t(11;19)(q21-22;p13.11)	CRTC3	MAML2	<1%	Fehr et al. Genes Chromosomes Cancer 2008
Dominant Negative Fusions				
Aggressive Midline Carcinoma				
t(15;19)(q13;p13.1)	BRD4	NUT	~66%	French et al. Cancer Res 2003; French et al. Am J Pathol 2001
t(9;15)(q34;q13)	BRD3	NUT	~10%	French et al. Oncogene 2008
Follicular Thyroid Carcinoma				
t(2,3)(q13;p25)	PAX8	PPARg	25-50%	Kroll et al. Science 2000

* prevalence of RET translocations depends on age and radiation exposure

Table 2**5' Binding Partners in Ets Fusions**

Ets fusions in prostate cancer exhibit a variety of 5' binding partners that drive overexpression of the Ets transcription factors. Accounting for approximately 90% of these, TMPRSS2-ERG is the most common of the known fusions, followed by TMPRSS2-ETV1. Other fusions feature prostate-specific genes (KLK2, C15orf21, CANT1, SLC45A3), endogenous retroviral elements (HERV_K_22q11.23, FLJ35294), a fatty-acid chain ligase (ACSL3), a DEAD box helicase (DDX5) and a housekeeping gene (HNRPA2B1). With the exception of HNRPA2B1-ETV1, C15ORF21-ETV1, and DDX5-ETV4, all of the 5' partners display androgen-responsive upregulation.

5' Fusion Partners in Prostate Cancer		
5' Binding Partner	Description	References
TMPRSS2	Androgen-regulated transmembrane serine protease. Fuses with ERG, ETV1, ETV4, and ETV5.	Tomlins et al. Science 2005 Helgeson et al. Cancer Res 2008; Han et al. Cancer Res 2008
HERV_K_22q11.23	An endogenous retroviral element. Fuses with ETV1.	Tomlins et al. Nature 2007
C15orf21	A prostate-specific and androgen-repressed gene. Fuses with ETV1.	Tomlins et al. Nature 2007
HNRPA2B1	A prominent housekeeping gene. Fuses with ETV1.	Tomlins et al. Nature 2007
ACSL3	An isozyme of the long-chain fatty-acid coenzyme A ligase family. Fuses with ETV1	Attard et al. Br J Cancer 2008
FLJ35294	An endogenous retroviral element (HERVK_17p13.1). Fuses with ETV1	Han et al. Cancer Res 2008
DDX5	Putative RNA helicase with a DEAD box polypeptide. Fuses with ETV4.	Han et al. Cancer Res 2008
KLK2	Prostate-specific, androgen-regulated gene. Fuses with ETV4.	Hermans et al. Cancer Res 2008
CANT1	Prostate-specific, androgen-regulated gene. Fuses with ETV4.	Hermans et al. Cancer Res 2008
SLC45A3	Prostate-specific androgen-induced gene. Fuses with ERG, ETV1 and ETV5.	Tomlins et al. Nature 2007; Helgeson et al. Cancer Res 2008; Han et al. Cancer Res 2008