More than 20 different fusion genes have been discovered in prostate cancer (Table 1). The most remarkable of these discoveries was the very first, TMPRSS2-ERG, which is found in more than half of all human prostate cancers (1). Whereas the TMPRSS2-ERG fusion is the most common gene fusion in any solid tumor, the other reported fusion genes in prostate cancer are found in rare subgroups or in individual tumors. In this issue of Cancer Discovery, Wang and colleagues (2) report on the discovery of yet another fusion gene in a prostate cancer cell line, a fusion between UBE2L3 and KRAS. This gene fusion originates from breakpoints associated with gene amplifications and is overexpressed. The authors provide functional data supporting the importance of the fusion gene in the DU145 cancer cell line as well as initial clinical validation of the relevance of KRAS rearrangements in rare cases of metastatic end-stage disease. A novel gene fusion in cancer is an exciting finding because it may open up possibilities for diagnosis and therapy. This gene fusion is also of potential interest because it involves a major cancer gene, KRAS. However, this discovery is still in an early stage, and further efforts are required to confirm its functional and clinical importance.

Wang and colleagues found the UBE2L3-KRAS gene through a novel approach called amplification breakpoint ranking and assembly analysis, which is based on the matching of genomic copy number breakpoint locations and levels of amplification in array-based comparative genomic hybridization or single-nucleotide polymorphism array data. This technology may be powerful for the selection of clinical samples for fusion gene search. One could argue, however, that RNA-sequencing technologies have recently evolved to such an extent that it is now possible to quickly and reliably score gene fusions directly from the sequencing data (3–5). In this context, integrated genomic datasets containing gene expression, copy number data, and genomic or cDNA sequence information from the same samples are highly valuable. For example, such an integrated approach helped Wang and colleagues to confirm and support the concept that high-level DNA amplifications in cancer contain complex rearrangements and gene fusions (5–7). The presence of gene fusions within and between amplicons suggests that these types of genetic events may also drive or at least modulate the clonal evolution of cancer and that gene copy number gains and losses are not the only events that confer selective advantage of unbalanced genomic rearrangements.

How will the UBE2L3–KRAS gene rearrangement change our views of prostate cancer causation, diagnosis, and treatment? On the basis of the clinical data presented by Wang and colleagues, it appears as though the impact will be limited. The first and foremost limitation is the prevalence of the gene fusion. KRAS rearrangements were not found in any of the 259 primary prostate cancers examined and were detected in only 2 of 62 (3%) metastatic prostate cancers. This observation suggests that the KRAS rearrangements are associated with late stages of tumor progression and metastasis, not with the onset of prostate cancer. However, taken together with the data from the DU145 prostate cancer cell line, KRAS rearrangements should qualify as a recurrent genetic event in prostate cancer. The authors previously reported that advanced prostate tumors occasionally (1%-2%) harbor rearrangements of Braf and Raf1 (3). This finding supports the involvement of Ras family signaling in a small subset of prostate cancers. Obviously, because late-stage recurrent cancers are heterogeneous and highly complex, further work is needed to determine the clinical significance of the UBE2L3–KRAS rearrangement and its potential diagnostic and therapeutic implications.

### Table 1. Prostate cancer fusion genes reported in the literature

<table>
<thead>
<tr>
<th>Fusion gene</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMPRSS2-ERG</td>
<td>Tomlins et al. (1)</td>
</tr>
<tr>
<td>TMPRSS2-ETV5, SLC45A3-ETV5</td>
<td>Hermans et al. (12)</td>
</tr>
<tr>
<td>KLK2-ETV4, CANTI-ETV4</td>
<td>Han et al. (13)</td>
</tr>
<tr>
<td>SLC45A3-ERG, SLC45A3-ETV1, TMPRSS2-ETV1, HERVK_22q11.23-ETV1, C15orf21-ETV1, HNRPA2B1-ETV1, FLJ35294-ETV1, CANTI-ETV4, DDX5-ETV4, TMPRSS2-ETV4</td>
<td></td>
</tr>
<tr>
<td>NDRG1-ERG</td>
<td>Pflueger et al. (14)</td>
</tr>
<tr>
<td>SLC45A3-BRAF, ESRP1-RAF1</td>
<td>Palanisamy et al. (3)</td>
</tr>
<tr>
<td>Complex ETV1 rearrangements</td>
<td>Pflueger et al. (4)</td>
</tr>
<tr>
<td>7 previously unreported gene fusions, including KLK2-ETV1 and FKB55-ERG</td>
<td></td>
</tr>
<tr>
<td>UBE2L3-KRAS</td>
<td>Wang et al. (2)</td>
</tr>
</tbody>
</table>
unstable genetically and because they harbor many other rearrangements, the independent role of KRAS changes in late-stage prostate cancers remains to be determined.

Wang and colleagues provide the first evidence of the potential functional importance of the KRAS fusion gene (2), but many questions regarding its biological impact remain unanswered. When the gene fusion was knocked down in DU145 prostate cancer cells, cell growth slowed down and a significant reduction in tumorigenicity was observed in vivo. Overexpression of the UBE2L3-KRAS gene fusion in the mouse fibroblast NIH-3T3 cell line and in human RWPE prostate epithelial cells caused signs of transformation. Although the functional evidence seems highly promising, further exploration is needed to identify the specific impact of rearrangements on cellular KRAS signaling. The different cell line models used in the study showed a differential activation of downstream signaling pathways, such as MEK-ERK and AKT/p38 MAPK. Of interest, the latter route is typically not associated with KRAS signaling in cancer. Another question left open by the current study is whether KRAS is always fused to UBE2L3 in prostate cancer, or if the 5′ partner is interchangeable. UBE2L3 as the 5′ partner could affect the ubiquitin-proteasome-mediated turnover of the UBE2L3-KRAS fusion. However, as previously reported in prostate cancer (4, 6) and seen for breast cancer or melanoma fusion genes (5, 7), some fusion 5′ partner genes seem to serve solely as promoter donors, leading to ectopic, deregulated expression of the target gene. Considering the well-established oncogenic potential of KRAS, one might anticipate that a variety of 5′ fusion partners would be involved. However, the lack of previous observations of such gene fusions in any malignancy suggests that this is not a common event.

A lot of excitement currently focuses on the small subset of non-small cell lung cancers that harbor the EML4-ALK gene fusion (8). The 4% frequency of this gene fusion is not that different from the frequency of the KRAS rearrangements reported by Wang and colleagues, except that the latter changes are found only in the less common metastatic and recurrent disease type. The discovery of the EML4-ALK gene fusion, however, has rapidly led to remarkable breakthroughs in treating these lung cancers with anaplastic lymphoma kinase inhibitors (8). Therefore, common cancers are increasingly divided into smaller and smaller subsets, each defined by unique genetic abnormalities that may be discovered only by deep genomic and transcriptomic exploration and sophisticated bioinformatic analyses. Once large-scale projects like the International Cancer Genome Initiative (www.icgc.org) are completed, it will be possible to formulate an overview of all the recurrent events across all types of cancers. This resource will help to sort out the significance of rare events and their potential clinical and therapeutic significance. Clinical associations of very rare fusion genes may be difficult to establish owing to the large number of patients who would need to be studied. One could argue, however, that overexpressed fusion genes are more likely to be pathogenic than are rearrangements found only at the genomic DNA level.

The UBE2L3-KRAS fusion gene discovery certainly provides a new addition to the growing catalog of prostate cancer genomic alterations. As noted previously, more than 20 different fusion gene events in prostate cancer have been reported (Table 1), and the number is likely to continue to grow rapidly. It will also be interesting to see whether a large number of individual fusion genes will be discovered in other solid tumor types. Preliminary evidence in breast cancer (5) and melanoma (7) suggests that this may well be the case. Recurrent fusion genes, such as TMPRSS2-ERG, may be uncommon, but individual rare gene fusions occur very frequently. Even rare changes may sometimes provide insights into unexpected therapeutic opportunities as well as starting points for the development of patient-specific biomarkers for noninvasive monitoring of tumor burden, for example, from plasma samples of cancer patients (9, 10).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Cancers Unexpected Rare Encounters in Late-Stage Prostate Cancers

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