Molecular Pathology Abstracts, 1/18

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Importance of interstitial genes that exist between gene fusion partners in prostate cancer

Prostate cancer is one of the most common cancers affecting men, yet understanding of the disease's development and progression is limited. One of the most effective ways to stratify treatment and outcomes is based on pathology review of prostate biopsies, though the application of molecular testing to these samples is increasing. The medical community has analyzed numerous genomic alterations, including gene fusions, deletions, and mutations, in prostate cancer and generated molecular panels to help assess risk for men with prostate cancer. However, the prognostic impact of the most common gene fusion in prostate cancer, *TMPRSS2-ERG*, has remained elusive. *ERG* is a member of the ETS family of transcription factors that also includes *ETV1* and *ETV4*, which are located on separate chromosomes. The ETS family of transcription factors is driven in prostate cancer through the activity of the androgen-responsive *TMPRSS2* gene that is fused to the 5' region of ETS family members. However, findings indicate that the resultant ERG overexpression from this gene fusion is not prognostic for biochemical recurrence or disease-specific survival following radical prostatectomy. So why is *TMPRSS2-ERG* gene fusion so prevalent in prostate cancer, and what does it mean? Murphy, et al., examined a previously understudied element related to gene fusion that may help stratify men whose prostate cancers harbor *TMPRSS2-ERG* fusion. The study focused on dissecting two types of mechanisms that underlie gene fusion—one that involves an interstitial deletion between the *TMPRSS2* and *ERG* genes that eliminates a 3-Mb gene region between these two genes, and an alternative mechanism of insertional recombination that retains the interstitial gene region. Both mechanisms result in identical gene fusion products, but only a subset of cancers retains the interstitial genes. To test if the interstitial genes influenced outcomes, the authors used mate pair next-generation sequencing on 133 prostate cancers, from radical prostatectomy specimens, that included low-risk Gleason score 6 prostate cancers and higher risk Gleason score 7 and above prostate cancers. They compared the retention of interstitial genes to outcomes, including biochemical recurrence. The results indicated that *ERG* fusions that retained the interstitial gene region were more common in low-risk prostate cancer, suggesting a potential tumor-suppressor function of one or more genes within the interstitial region. Furthermore, the presence of retained interstitial genes was associated with a reduced risk of biochemical recurrence. The authors concluded that their study demonstrates that more detailed analysis of *TMPRSS2-ERG* events may be the key to better understanding the biology of prostate cancer and predicting progression in prostate cancer patients. Additional studies that evaluate the retention and role of interstitial genes in *TMPRSS2-ERG* fusion-positive prostate cancers in biopsy specimens will be critical to stratifying patients early in the treatment paradigm.

Murphy SJ, Kosari F, Karnes J, et al. Retention of interstitial genes between *TMPRSS2* and *ERG* is associated with low-risk prostate cancer. *Cancer Res.* 2017;77:6157–6167.

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Predicting adverse psychological experiences with genome-wide testing

Since 2017, when direct-to-consumer genomic testing was beginning to be used widely, several groups have analyzed the psychological impact of such testing on the consumers of these tests. In several studies, negative psychological effects, such as clinically meaningful test-related distress or a clinically reliable change in anxiety levels, occurred in less than four percent of patients. However, other studies have shown much higher rates of distress and anxiety following genomic testing, especially when the test involves identifying genomic alterations that have higher penetrance and relative risk and a broader impact on a recipient's family. One example is the reporting of alterations in *BRCA1* and *BRCA2* genes, with alterations indicating an inherited risk for developing breast, ovarian, and many other cancers. To better understand the impact of genomic testing on consumers, Broady, et al., performed a secondary analysis of data from the Scripps Genomic Health Initiative (SGHI). The latter analyzed data on 2,037 people who had used commercially available testing for 23 common, genetically complex diseases to determine their personalized disease risk. The secondary analysis expanded on prior work from the SGHI study in order to assess adverse psychological outcomes. These outcomes were classified as "distress response," in which the study participant developed significant anxiety or distress, or both, as a result of the genomic test, or "psychologically sensitive," in which participants were considered to have pre-existing sensitivity related to elevated anxiety about the genomic test. The study then correlated development of an adverse psychological outcome with demographic variables, genomic risk results, pretest concerns regarding participation in genomic testing, reaction to genomic risk result reports, and other factors. Using two published scales of adverse psychological outcomes, the Impact of Event Scale-Revised (IES-R) and State-Trait Anxiety Inventory (STAI), 6.4 percent of participants showed a distress response and 21.2 percent were defined as psychologically sensitive. A distress response was significantly associated with a personal or family history of restless leg syndrome. By contrast, younger age, higher rates of pretest concerns, or a personal or family history of Alzheimer's disease were significantly associated with psychologically sensitive subjects. Psychologically sensitive participants indicated major concerns regarding the discovery of disease risk, their anticipated initial response, the quality and reliability of genomic testing, and potential privacy issues. However, when compared with their respective control groups, those with a distress response or who were psychologically sensitive were not more likely to follow up with their physician or use a free genetic counseling service once they received their test results. While this study has several limitations related to population sampling and the predictive value of common variants for complex disease traits, the results support the value of identifying recipients of genomic testing who would benefit from special attention to reduce anxiety prior to genomic testing and when receiving results.

Broady KM, Ormond KE, Topol EJ, et al. Prediction of adverse psychological experiences surrounding genome-wide profiling for disease risk. *J Community Genet.* 2017. doi:10.1007/s12687-017-0339-z.

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