Gene Cell Tissue. 2014 November; 1(3): e23703. DOI: 10.17795/gct-23703

Published online 2014 October 29. **Letter**

The Role of RNASEL Mutation in the Complex Genetic Landscape of Prostate Adenocarcinoma

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Received: September 17, 2014; **Accepted:** September 30, 2014

Keywords: Prostate; adenocarcinoma; 2-5A-dependent ribonuclease; Genome-Wide Association Study

Dear Editor

The incidence rate of prostate adenocarcinoma was an estimated 233,000 U.S men in 2014 and 1.11 million men globally in 2012, making it the second most common cancer in both the U.S and globally as well as a significant public health priority (1). Well-described as showing strong familial clustering, the genetic basis of prostate cancer has been further elucidated over the past 60 years. The first discovered prostate cancer susceptibility locus, namely hereditary prostate cancer 1 (HPC1), located at 1q24-25, was identified in large families with early-onset hereditary prostate cancer (2). Later studies helped to identify multiple linked genetic loci, including HPC1, HPC2 (17p11), PCAP (1q42.2-q43), HPCX (Xq27-q28), CAPB (1p36), and HPC20 (20q13) (3).

In the classic paper by Carpten et al. the tumor suppressor 2'-5'oligoadenylate (2-5A)-dependent RNase L (RNASEL) was cloned and found mutated in two HPC1-linked families (4). Upon activation, the interferon-induced ribonuclease RNASEL degrades cellular and viral RNA to make cells resistant to viral infection. These authors also showed RNASEL to be a germline mutation that could be detected in lymphoblasts as well as dissected tissue, thus setting the possibility of a screening tool for high-risk adult prostate cancer. Early studies suggested that RNASEL was implicated in up to 13% of all prostate cancer cases, and certain mutations (i.e. Arg462Gln) could impart up to a 50% greater risk of prostate cancer (5). Various mutations in RNASEL have been described to increase prostate cancer risk, including E262X, 471delAAAG, Arg463Gln, Asp541Glu, and Arg462Gln (6). Similarly, a variety of single nucleotide polymorphisms at the HPC1 locus and others can help explain up to 30% of familial prostate cancer risk (7).

In the previous issue of "Gene, Cell and Tissue", Seidabadi et al. further elucidated the role of Arg462Gln mutation of RNASEL within a pathology databank (8). Sequencing of paraffin-embedded prostate cancer tissue was compared to benign prostate pathology. In comparing their prostate cancer population to controls, the authors did not find a significant difference in wild type (82% vs. 87%), heterozygous mutations (14% vs. 13%), or homozygous mutations (2% vs. 0%). The authors are commended for helping to further validate this hypothesized mutation and better explain prostate cancer genetics. While these results were similar to the negative findings of some studies (9), they were distinct from those of other studies (5). Certainly, the difference in sample size of this study (n = 121) compared with the original study by Casey et al. (5) (n = 877) could have affected results. The differences in patient selection retrospective review of a tumor bank in the case of Seidabadi et al. (8) versus prospective, familial case-control subjects in the study by Casey et al. (5) may also have been a factor. Finally, the genetic pool of the cases, Iranian in Seidabadi et al. (8) vs. Midwest America in Casey et al., (5) could have had an effect. Thus, the results of the study by Seidabadi et al. (8) highlight the difficulty of understanding prostate cancer genetics.

Genetic studies in prostate cancer are complicated by a number of issues, including 1) the incidence of sporadic disease vs. familial disease, whose clinical presentations can be similar, 2) clinic pathological variation of disease, 3) different methods of identifying familial disease, 4) variation in methods to perform and statistically analyze linkage studies, and 5) population variation in genetics. These features make mapping of genetic risk factors in prostate cancer especially challenging and somewhat unique from other types of cancers. Many of these limitations can be overcome by coordinated, large-scale studies that account for clinically relevant variables. A recent large-scale genome-wide association study of 87,040 in-

dividuals helped to elucidate 23 new susceptibility loci explaining up to 33% of familial risk (10). Such is the capability of larger, well-powered studies. Certainly, larger groups of samples from a variety of sources would be needed for identification of mutation type and cancer risk; however, efforts to curb the heterogeneity of cancer should be used. Clinical stratification of patients using monitored morbidity and mortality, noting genetic pools for genomic studies, demarcation of familial vs. sporadic cases, as well as determining Gleason scores and other pathological markers can be useful to compare prostate cancers properly. Only after a concerted effort could the importance of mutated prostate cancer genes be identified.

Acknowledgements

Special thanks to Kristin Kraus, MSc, for editorial assistance with this paper.

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