Asian Journal of Andrology (2016) 18, 530–532

www.asiaandro.com; www.ajandrology.com

Open Access

INVITED RESEARCH HIGHLIGHT

Prostate Cancer

HOXB13 and other high penetrant genes for prostate cancer

Patrick G Pilie[1], Veda N Giri[2], Kathleen A Cooney[3]

Asian Journal of Andrology (2016) **18**, 530–532; doi: 10.4103/1008-682X.175785; published online: 1 April 2016

Cancer initiation and progression is the result of an accumulation of mutations in key tumor suppressor genes, mismatch repair genes, or oncogenes, which impact cancer cell growth, death, and differentiation. Mutations occurring in cancer tissue are termed somatic; whereas, heritable mutations that may be passed onto subsequent generations occur in germline DNA. It is these germline mutations that can lead to cancer family syndromes whereby family members carrying a deleterious germline mutation have an increased susceptibility to certain cancer phenotypes. Common features of hereditary cancer syndromes include early age-of-onset, multiple affected generations, rare tumor types, and/or multiple primary malignancies. Approximately, 5%–10% of all common cancers, including prostate cancer, have a hereditary component and are attributable to highly penetrant germline mutations.[1] Across all cancer types, known cancer susceptibility syndromes number >100; however, it is important to note that mutations in high-penetrance genes explain only a fraction of heritable cancers.[2] Well-known examples of hereditary cancer syndromes include Lynch (HNPCC), Cowden (PHTS), Li-Fraumeni, and Hereditary Breast and Ovarian Cancer (HBOC) syndromes, which are attributable to mutations in mismatch repair genes, *PTEN*, *p53*, and *BRCA1/2*, respectively.[3]

Prostate cancer has been shown to cluster within families and exhibit Mendelian inheritance patterns.[4] Family history of prostate cancer has been shown to increase prostate cancer risk whereby the risk is influenced by: (1) the number of affected family members, (2) first degree affected relatives compared to those who are more distantly related, (3) the presence of early onset cancers in a pedigree (typically men diagnosed at or before age 55).[5,6] Despite this recognized familial component, identification of highly penetrant genes in hereditary prostate cancer has proven challenging. However, it is becoming increasingly important to identify these individuals with germline mutations at higher risk for prostate cancer, given that there are no uniformly recommended prostate cancer screening practices for the general population of men in the United States.[7]

Early genome-wide linkage studies focusing on families with a history of hereditary prostate cancer resulted in the identification of a number of potential candidate loci, many of which were not confirmed in replication studies. The University of Michigan Prostate Cancer Genetics Project (PCGP) conducted a genome-wide linkage scan on 175 prostate cancer pedigrees and identified a novel linkage on chromosome 17q near *BRCA1*.[8–10] *BRCA1* was excluded as the cause of this linkage signal through mutation screening in families with linkage evidence to chromosome 17q markers.[11] Chromosome 17q remained a candidate linkage region when linkage studies were combined including research conducted by the International Consortium for Prostate Cancer Genetics of ICPCG.[9] The candidate region was subsequently narrowed by fine-mapping to an approximately 10 cM region and notably the 147 families with >4 cases of prostate cancer, and evidence of early-onset prostate cancer diagnosis provided the strongest evidence for linkage to this region (LOD = 5.49 near D17S1820).[12] With the advent of next generation sequencing technologies, sequencing of all 202 genes in the 1-LOD support interval was performed on germline DNA from the youngest family member from 94 multiplex prostate cancer families from the PCGP and Johns Hopkins University selected on the basis of linkage evidence to the candidate region.[13] A recurrent mutation was identified in the *HOXB13* gene, a member of the homebox gene family, which resulted in a nonconservative substitution of glutamic acid for glycine (G84E). The HOXB13 protein in its normal function plays an important role in urogenital development and maintains high expression levels in the normal prostate into adulthood. Interestingly, all men with prostate cancer in the four pedigrees from the probands with the G84E mutation carried the same mutation. The team went onto genotype a large number (over 5000) of additional prostate cancer cases to define the frequency of the mutation in various clinical subsets. The carrier frequency observed in men with a positive family history (2.2%) was identical to men with an early-age of prostate cancer diagnosis (2.2%), and the highest carrier frequency was observed in the subset of men with both a positive family history and early-onset disease (3.1%). In contrast, in men diagnosed with prostate cancer above the age of 65, a frequency of 0.65% of *HOXB13* G84E carriers was observed. This seminal study was the first to show a recurrent, highly penetrant gene mutation co-segregating predominantly with an early-onset, hereditary prostate cancer phenotype.[13]

There have been many follow-up studies to demonstrate the contributions of germline *HOXB13* mutations to prostate cancer. The *HOXB13* G84E mutation has only been in individuals of European descent, although other mutations in this gene have been observed identified in African American and Chinese men with prostate cancer.[13,14]

[1]Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Department of Medical Oncology, Sidney Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA, USA; [3]Division of Hematology/Oncology, Department of Internal Medicine, University of Michigan Medical School and The University of Michigan Comprehensive Cancer Center, Ann Arbor, MI, USA. Correspondence: Dr. KA Cooney (Kcooney@med.umich.edu)

A follow-up study conducted by the ICPCG demonstrated that approximately 5% of hereditary prostate cancer families are likely in the setting of *HOXB13* mutations.[15] In this report, it was noted that the *HOXB13* G84E mutation occurs on a common haplotype suggesting a founder effect. Genotyping of 3508 men in the REDUCE trial showed the *HOXB13* G84E mutation was most prevalent in Northern European populations (1.06%), particularly in those from Finland and Sweden with a family history of prostate cancer.[16]

In a multi-institutional North American study of 9559 men with prostate cancer who underwent radical prostatectomy, 1.3% or 128 men were carriers of the G84E mutation with those carriers being more likely to have a family history of prostate cancer and be diagnosed at a younger age than noncarriers.[17] A similar prevalence and co-segregation with prostate cancer was seen in a British cohort of 8518 men with prostate cancer (1.5%) with 5252 healthy controls (0.5%) conferring an overall 2.82-fold increased risk of prostate cancer in carriers, with an over 3-fold increased risk of early onset prostate cancer for carriers and 4.5-fold risk for those carriers with a family history of prostate cancer. However, mutation status was neither associated with any hallmarks of aggressive prostate cancer nor did it show any correlation with overall survival.[18] A recent study has also shown that the *HOXB13* G84E mutation may also confer an increased risk of leukemia and bladder cancer, which further implicates the mutation's role in carcinogenesis.[19] However, the carrier frequency in these unselected male samples from a single-institution's cancer biobank was low with only 49/9012 carrying the mutation (0.5%), and further studies need to be performed to understand the mutation's role in other cancer types.

While the increased risk of prostate cancer in individuals carrying the *HOXB13* G84E allele has been shown across multiple studies in European-descent populations, the molecular mechanism by which *HOXB13* G84E promotes prostate cancer development remains unknown. A study of 23 prostatectomy specimens from G84E mutation carriers showed frequent pseudohyperplastic-type features in addition to a markedly low prevalence of ERG(+) fusions when compared to specimens from noncarriers. These variant histopathologic characteristics point to a distinct underlying errant molecular pathway in tumors from mutation carriers. While mutational testing of HOXB13 is not currently a clinical standard of care, carrier status could have potential future implications for risk stratification, prevention, screening, and even personalized treatments for prostate cancer.

Mutations in the DNA damage repair pathway genes *BRCA1* and *BRCA2* are well known to confer a significantly increased risk of breast and ovarian cancer (HBOC). Large population studies of male *BRCA* carriers have shown that mutations in *BRCA2* confer a higher risk of prostate cancer ranging from 2.5 to 8.6 times compared to the general population;[20] however, mutations in *BRCA1* show a more modest increased risk of 3.5-fold in individuals under the age of 65 only.[21,22] A study of 2019 patients with prostate cancer including 18 *BRCA1* and 61 *BRCA2* carriers showed that *BRCA* carriers displayed a more aggressive prostate cancer phenotype. Those subjects harboring a *BRCA2* mutation were statistically significantly more likely to have disease that was Gleason ≥8, T3/T4 stage, nodal involvement, and metastases at the time of diagnoses when compared to noncarriers. The subgroup analysis for *BRCA1* carriers was not definitive due to the small sample size. In addition to these poor prognostic indicators seen in carriers, 5-year overall cause-specific survival (96% *vs* 82%) and metastasis-free survival (93% *vs* 77%) were better in noncarriers versus carriers, respectively.[21]

In a recent multi-institutional study of 150 biopsy specimens from men with metastatic castrate-resistant prostate cancer, 8% ($n = 12$) were found to have actionable pathogenic germline alterations. The majority of these germline mutations were in *BRCA2* and were more common in castrate-resistant prostate cancer compared to primary prostate cancer, further alluding to the aggressive nature of prostate cancer in *BRCA2* mutation carriers. The remaining germline mutations seen in this study also centered on the DNA repair pathway with mutations seen in *ATM* and *BRCA1*, highlighting the crucial role that the DNA repair pathway plays in prostate cancer initiation and progression.[23] The NCCN guidelines for Genetic/Familial High-Risk Assessment - Breast and Ovarian recommend that men with *BRCA2* mutations start prostate cancer screening at age 40 and that men with *BRCA1* consider the same.[24] Genetic testing can be considered in men with a personal history of prostate cancer of high Gleason score (≥7) in addition to a family history of ≥ 2 close blood relatives with breast and/or ovarian cancer and/or prostate cancer (Gleason ≥7) at any age.[24] A study of 146 men presenting for genetic testing validated the use of BRCAPRO model in predicting whether a man is a *BRCA* mutation carrier; however, this study included men with male breast cancer and/or a family history suspicious for HBOC.[25] Further studies need to be done to more accurately predict which men are at risk for carrying a DNA repair pathway mutation based on hereditary prostate cancer features and family history. In addition, identifying those individuals with prostate cancer who harbor germline and somatic DNA repair pathway mutations in genes such as *BRCA2* and *ATM* may have implications for targeted treatments. A multi-center phase II study of olaparib, an oral poly(ADP-ribose) polymerase inhibitor, in 298 germline *BRCA1/2* carriers included eight men with prostate cancer who had progressed on hormonal and at least one systemic therapy. Stable disease ≥8 weeks was observed in 25% of the subset with prostate cancer; however, grade ≥3 adverse events were reported in 54% of patients across cancer types.[26]

Other rare germline variants have been implicated in prostate cancer including mutations in mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, and *PMS2*) seen in Lynch syndrome. A study of 97 prostate cancer cases in 198 Lynch syndrome families showed a cumulative risk of prostate cancer of 6.30% at age 60 and 30.0% at age 80 compared to a general population risk of 2.59% and 17.8%, respectively, with an overall prostate cancer hazard ratio of 1.99 (95% CI: 1.31–3.03).[27] Although these germline events are uncommon and do not account for a significant portion of prostate cancer cases, these rare genetic lesions can identify pathways in more common sporadic prostate cancer.

REFERENCES

1 Nagy R, Sweet K, Eng C. Highly penetrant hereditary cancer syndromes. *Oncogene* 2004; 23: 6445–70.
2 Stadler ZK, Schrader KA, Vijai J, Robson ME, Offit K. Cancer genomics and inherited risk. *J Clin Oncol* 2014; 32: 687–98.
3 Foulkes WD. Inherited susceptibility to common cancers. *N Engl J Med* 2008; 359: 2143–53.
4 Carter BS, Beaty TH, Steinberg GD, Childs B, Walsh PC. Mendelian inheritance of familial prostate cancer. *Proc Natl Acad Sci U S A* 1992; 89: 3367–71.
5 Zeegers MP, Jellema A, Ostrer H. Empiric risk of prostate carcinoma for relatives of patients with prostate carcinoma: a meta-analysis. *Cancer* 2003; 97: 1894–903.
6 Hemminki K, Czene K. Age specific and attributable risks of familial prostate carcinoma from the family-cancer database. *Cancer* 2002; 95: 1346–53.
7 USPTF. Final Recommendation Statement: Prostate Cancer; 2012. Available from: http://www.uspreventiveservicestaskforce.org/. [Last accessed on 2015 Aug 25].
8 Gillanders EM, Xu J, Chang BL, Lange EM, Wiklund F, *et al*. Combined genome-wide scan for prostate cancer susceptibility genes. *J Natl Cancer Inst* 2004; 96: 1240–7.
9 Xu J, Dimitrov L, Chang BL, Adams TS, Turner AR,

et al. A combined genomewide linkage scan of 1,233 families for prostate cancer-susceptibility genes conducted by the international consortium for prostate cancer genetics. *Am J Hum Genet* 2005; 77: 219–29.

10 Lange EM, Gillanders EM, Davis CC, Brown WM, Campbell JK, *et al*. Genome-wide scan for prostate cancer susceptibility genes using families from the University of Michigan prostate cancer genetics project finds evidence for linkage on chromosome 17 near BRCA1. *Prostate* 2003; 57: 326–34.

11 Zuhlke KA, Madeoy JJ, Beebe-Dimmer J, White KA, Griffin A, *et al*. Truncating BRCA1 mutations are uncommon in a cohort of hereditary prostate cancer families with evidence of linkage to 17q markers. *Clin Cancer Res* 2004; 10: 5975–80.

12 Lange EM, Robbins CM, Gillanders EM, Zheng SL, Xu J, *et al*. Fine-mapping the putative chromosome 17q21-22 prostate cancer susceptibility gene to a 10 cM region based on linkage analysis. *Hum Genet* 2007; 121: 49–55.

13 Ewing CM, Ray AM, Lange EM, Zuhlke KA, Robbins CM, *et al*. Germline mutations in HOXB13 and prostate-cancer risk. *N Engl J Med* 2012; 366: 141–9.

14 Lin X, Qu L, Chen Z, Xu C, Ye D, *et al*. A novel germline mutation in HOXB13 is associated with prostate cancer risk in Chinese men. *Prostate* 2013; 73: 169–75.

15 Xu J, Lange EM, Lu L, Zheng SL, Wang Z, *et al*. HOXB13 is a susceptibility gene for prostate cancer: results from the International Consortium for Prostate Cancer Genetics (ICPCG). *Hum Genet* 2013; 132: 5–14.

16 Chen Z, Greenwood C, Isaacs WB, Foulkes WD, Sun J, *et al*. The G84E mutation of HOXB13 is associated with increased risk for prostate cancer: results from the REDUCE trial. *Carcinogenesis* 2013; 34: 1260–4.

17 Beebe-Dimmer JL, Isaacs WB, Zuhlke KA, Yee C, Walsh PC, *et al*. Prevalence of the HOXB13 G84E prostate cancer risk allele in men treated with radical prostatectomy. *BJU Int* 2014; 113: 830–5.

18 Kote-Jarai Z, Mikropoulos C, Leongamornlert DA, Dadaev T, Tymrakiewicz M, *et al*. Prevalence of the HOXB13 G84E germline mutation in British men and correlation with prostate cancer risk, tumour characteristics and clinical outcomes. *Ann Oncol* 2015; 26: 756–61.

19 Beebe-Dimmer JL, Hathcock M, Yee C, Okoth LA, Ewing CM, *et al*. The HOXB13 G84E mutation is associated with an increased risk for prostate cancer and other malignancies. *Cancer Epidemiol Biomarkers Prev* 2015; 73: 169–75.

20 Mersch J, Jackson MA, Park M, Nebgen D, Peterson SK, *et al*. Cancers associated with BRCA1 and BRCA2 mutations other than breast and ovarian. Cancer 2015;121:269-275. *Cancer* 2015; 121: 2474–5.

21 Castro E, Goh C, Olmos D, Saunders E, Leongamornlert D, *et al*. Germline BRCA mutations are associated with higher risk of nodal involvement, distant metastasis, and poor survival outcomes in prostate cancer. *J Clin Oncol* 2013; 31: 1748–57.

22 Castro E, Eeles R. The role of BRCA1 and BRCA2 in prostate cancer. *Asian J Androl* 2012; 14: 409–14.

23 Robinson D, Van Allen EM, Wu YM, Schultz N, Lonigro RJ, *et al*. Integrative clinical genomics of advanced prostate cancer. *Cell* 2015; 161: 1215–28.

24 National Comprehensive Cancer Network. Genetic/Familial High Risk Assessment: Breast and Ovarian. Ver. 1. Fort Washington, PA; 2016. Available from: http://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf. [Last accessed on 2016 Mar 03].

25 Mitri ZI, Jackson M, Garby C, Song J, Giordano SH, *et al*. BRCAPRO 6.0 model validation in male patients presenting for BRCA testing. *Oncologist* 2015; 20: 593–7.

26 Kaufman B, Shapira-Frommer R, Schmutzler RK, Audeh MW, Friedlander M, *et al*. Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. *J Clin Oncol* 2015; 33: 244–50.

27 Raymond VM, Mukherjee B, Wang F, Huang SC, Stoffel EM, *et al*. Elevated risk of prostate cancer among men with Lynch syndrome. *J Clin Oncol* 2013; 31: 1713–8.