Updated insights into genetic contribution to prostate cancer predisposition: focus on HOXB13

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This presentation for the Philadelphia Prostate Cancer Consensus 2019 will focus on recent findings regarding the role of HOXB13 as a prostate cancer susceptibility gene. Factors affecting the frequency of HOXB13 mutations in different prostate cancer populations will be reviewed. A number of these factors are relevant for prostate cancer susceptibility genes in general.

Key Words: high penetrance genes, prostate cancer, germline

In early 2012 the identification of the first bona fide prostate cancer-specific susceptibility gene, *HOXB13* was reported.[1] Using linkage analyses in prostate cancer families, a recurrent but rare missense change, *G84E*, was identified in the *HOXB13* gene on 17q21. In an analysis of germline DNA from over 5,000 prostate cancer cases and controls, we found that the frequency of *G84E* was significantly higher in cases (1.4%) than controls (0.1%-0.4%). An enrichment of *G84E* was found in prostate cancer patients who were diagnosed at early age (eg. under 55) and with a positive family history of prostate cancer. These finding have been consistently confirmed by many labs around the world, with ORs for prostate cancer varying from 2-15 fold. Through combined analyses of different study populations in the International Consortium for Prostate Cancer Genetics (ICPCG), the observation was made that the most common mutation in *HOXB13* in US men, *G84E*, had the highest frequency in individuals of Nordic descent.[2] Indeed, as many as 8%-10% of Swedish[3] and Finnish[4] men with family history positive prostate cancer diagnosed at an early age carry a *G84E HOXB13* mutation, compared to ~1% or less in unaffected men. A critical additional finding was that all *G84E* mutation carriers shared a common haplotype,[2] i.e., they are all descended from a common founder, presumably of Swedish or Finnish origin. Founder mutations in *HOXB13* have been found to be associated with prostate cancer risk in other populations, including *G132E* in Japanese men,[5] and *G135E* in Chinese men.[6] Each of these mutations, substituting a glutamic acid for glycine at amino acid positions 84, 132, and 135, respectively, lie in one of two highly conserved domains in the *HOXB13* protein which are responsible for binding to the homeobox cofactor, MEIS,[7,8] suggesting an alteration of this binding as a mechanistic feature of the cancer promoting action of these G to E variants.

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Observations characterizing *HOXB13* and its role in prostate carcinogenesis include:

1. *HOXB13* expression is highly prostate specific where it is necessary for normal prostate development;[9] this expression is maintained throughout initiation and progression of prostate cancer.
2. *HOXB13* interacts with AR to modulate the expression of various androgen responsive genes.[10]
3. As indicated above, three critical factors affect the frequency, and thus importance of *G84E* as a susceptibility gene:
   a. Age of diagnosis: men diagnosed under age 55 have the highest frequency of *G84E*. In men diagnosed over age 70, the frequency is not significantly different from the general population. This earlier age of onset associated with this mutation is similar to that seen in other cancers that are due to germline variants, eg, *BRCA1* and breast cancer, and *APC* and colorectal cancer.
   b. Family history: the frequency of *G84E* is elevated in men with first degree relatives affected with prostate cancer and is highest in men diagnosed both at an early age and with a family history of prostate cancer.
   c. Ancestry: individuals of Swedish and Finnish ancestry have the highest population frequencies of *G84E* due to a founder mutation; in men of African and eastern European descent, *G84E* is extremely rare. Other *HOXB13* founder mutations are important in Chinese and Japanese, and possibly others yet to be found.
4. While not completely consistent, most studies of clinicopathologic variables do not find any differences in prostate cancer between carriers and noncarriers of *G84E*. What is clear is that the association of *G84E* and prostate cancer is equally strong in men with high- and low-risk prostate cancer, i.e. carriers of *G84E* are at increased risk of the full spectrum of prostate cancer, including high risk, lethal disease.
5. *G84E* can be highly penetrant: the penetrance of *G84E* varies with ancestry, age at diagnosis, family history, and year of birth.[11] Estimates range from 40% to 60% by age 85, and almost complete penetrance in men who have a strong family history of early onset prostate cancer.[3,11]
6. Penetrance of *G84E* may also be modified by genetic risk score (GRS) derived from multiple prostate cancer risk-associated SNPs. In a large Swedish population-based study, the cumulative prostate cancer risk by age 80 years was 33% for *G84E* carriers. This risk increased to 48% if carriers also had higher polygenic risk score (top quartile).[3,12]

With respect to these last features of *HOXB13*, the *G84E* variant is reminiscent of more common prostate cancer risk SNPs. While most of these latter variants have a much smaller effect size on risk and are more common than *G84E*, they apparently share with *G84E* a strict association with prostate cancer initiation, not progression. Thus, the most useful application of *G84E*, as with the set of prostate cancer risk SNPs and GRS, is in early identification men at elevated risk for prostate cancer diagnosis, with subsequent early and more intense disease screening to detect (or prevent) clinically significant cancers at a time when they are still curable.

Disclosures

Dr. William B. Isaacs and Kathleen A. Cooney have ownership interest in a patent on HOXB13 as a genetic marker of prostate cancer risk, owned by Johns Hopkins and University of Michigan.
Dr. Jianfeng Xu has no disclosures. □

References

1. Ewing CM, Ray AM, Lange EM et al. Germline mutations in HOXB13 and prostate-cancer risk. *N Engl J Med* 2012;366(2):141-1499.
2. Xu J, Lange EM, Lu L et al. HOXB13 is a susceptibility gene for prostate cancer: results from the International Consortium for Prostate Cancer Genetics (ICPCG). International Consortium for Prostate Cancer Genetics. *Hum Genet* 2013;132(1):5-14.
3. Karlsson R, Aly M, Clements M et al. A population-based assessment of germline HOXB13 G84E mutation and prostate cancer risk. Eur Urol 2014;65(1):169-176.
4. Laitinen VH, Wahlfors T, Saaristo L et al. HOXB13 G84E mutation in Finland: population-based analysis of prostate, breast, and colorectal cancer risk. *Cancer Epidemiol Biomarkers Prev* 2013;22(3):452-460.
5. Momozawa Y, Iwasaki Y, Hirata M et al. Germline pathogenic variants in 7,636 Japanese patients with prostate cancer and 12,366 controls. *J Natl Cancer Inst* 2019 Jun 19. Epub ahead of print.
6. Lin X, Qu L, Chen Z et al. A novel germline mutation in HOXB13 is associated with prostate cancer risk in Chinese men. *Prostate* 2013;73(2):169-175.
7. Bhanvadia RR, VanOpstall C, Brechka H et al. MEIS1 and MEIS2 expression and prostate cancer progression: a role for HOXB13 binding partners in metastatic disease. *Clin Cancer Res* 2018;24(15):3668-3680.
8. Johng D, Torga G, Ewing CM et al. HOXB13 interaction with MEIS1 modifies proliferation and gene expression in prostate cancer. *Prostate* 2019;79(4):414-424.
9. Economides KD, Capecchi MR. Hoxb13 is required for normal differentiation and secretory function of the ventral prostate. *Development* 2003;130(10):2061-2069.
10. Norris JD, Chang CY, Wittmann BM et al. The homeodomain protein HOXB13 regulates the cellular response to androgens. *Mol Cell* 2009;36(3):405-416.
11. Nyberg T, Govindasami K, Leslie G et al. Homeobox B13 G84E mutation and prostate cancer risk. *Eur Urol* 2019;75(5):834-845.
12. Kote-Jarai Z, Mikropoulos C, Leongamornlert DA et al. Prevalence of the HOXB13 G84E germline mutation in British men and correlation with prostate cancer risk, tumour characteristics and clinical outcomes. UK Genetic Prostate Cancer Study Collaborators, and ProtecT Study Group. *Ann Oncol* 2015;26(4):756-761.