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# HOXB13 Mutations and Prostate Cancer Risk

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Conflicts of Interest

Dr. Cooney reports no conflicts of interest. However, Dr. Cooney has a patent application relating to the discovery of HOXB13 which is pending.

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For the first time, Storebjerg and colleagues describe the prevalence of the *HOXB13* G84E mutation in a Danish population and its association with prostate cancer risk and features indicative of clinically aggressive disease in a cohort of men undergoing radical prostatectomy. In this study, the prostate cancer risk mutation was observed in 0.49% of controls with an approximate 5-fold increase in risk of prostate cancer among carriers.(1) The homeobox transcription factor gene *HOXB13*, is located on the long arm of chromosome 17 (17q21), and belongs to a superfamily of genes considered critical to animal embryonic development, characterized by a highly-conserved DNA-binding domain. In 2012, our research team described the association of a rare recurrent *HOXB13* mutation, substituting adenine for guanine in the second position of codon 84 resulting in the replacement of glycine by glutamic acid, with prostate cancer and demonstrated that the carrier frequency was ~20 times higher among men with early-onset disease and multiple affected close relatives compared to men presumed without disease.(2) Since then, numerous studies have confirmed this association with estimates of risk overall varying from ~3- to 9-fold, and generally a greater risk observed among men diagnosed before age 60 and among those with a positive family history of disease among first degree relatives.(3) The G84E mutation is almost exclusively observed in men of Northern European descent with evidence suggesting that it is a relatively recent (circa 1790s) founder mutation in the population, and considered to be of moderate penetrance (estimated lifetime risk among carriers 35% to 65%).(4) The same germline mutation has also been preliminarily reported to be associated with

cancers of the breast, colon, bladder and leukemia, but requires further investigation. (5;6)

The findings from this study, both with respect to the prevalence of the mutation as well as its magnitude of association with prostate cancer, are comparable to prior reports in Northern European populations. Furthermore, among the 995 cases, the mutation frequency was significantly associated with features predictive of progression after surgery (high PSA, positive surgical margins, higher pathologic Gleason score and non-organ confined disease) suggesting that genetic evaluation of men with a strong family history would identify a subset of men that would benefit from early screening and intervention in the same manner as are male carriers of known founder mutations in *BRCA2*.(7) The observation between *HOXB13* and clinical features indicative of aggressive disease has been less consistent compared with studies of risk overall and the exact mechanism whereby the gene contributes to malignant progression in the prostate is not well-understood. There is some suggestion that the gene may operate both as a tumor suppressor, as early studies demonstrate its suppression of androgen receptor (AR) activity, and as an oncogene since *HOXB13* overexpression has been observed in androgen-independent tumors.(8)

Currently, most countries (including the United States) do not recommend use of PSA screening for men at average risk for prostate cancer. However, given the significant risk of prostate cancer in men carrying a single copy of the *HOXB13* G84E allele, should these male mutation carriers be screened for prostate cancer with PSA testing and digital rectal examination? If so, how we identify these men and at what age should testing commence? Unfortunately, many G84E carriers may not be identified by family history which raises the question about when is the risk of disease significant enough to warrant population level testing? Since Nordic countries including Denmark have a higher frequency of *HOXB13* G84E allele in the general population, research directed

toward understanding the benefit of genetic testing followed by prostate cancer early detection strategies should be considered.



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