



Words of Wisdom

Re: Germline Mutations in *HOXB13* and Prostate-Cancer Risk

Ewing CM, Ray AM, Lange EM, et al

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Experts' summary:

The germline DNA of 94 patients with personal and familial prostate cancer (PCa) history was sequenced in the 17q21–22 region. A rare but recurrent mutation (G84E) affecting the homeobox B13 (*HOXB13*) gene was carried by four of these men. The authors investigated the families of these four probands and found that all 18 males with family disease had the G84E mutation. They looked for the newly documented mutation in two independent populations: 5083 subjects with PCa and 1404 control subjects. The G84E mutation was found in 1.4% of men with PCa versus 0.1% of the controls ($p = 8.5 \times 10^{-7}$). The mutation was significantly more exhibited in men with early-onset familial PCa (3.1%) compared to those with late-onset nonfamilial PCa (0.6%) ($p = 2.0 \times 10^{-6}$).

Experts' comments:

The *HOXB13* gene encodes a transcription factor for prostate carcinogenesis. The G84E mutation, now also identified as rs138213197, is novel and has not been reported in other gene-sequencing databases. Although it is rare, the mutation is the first major genetic variant associated with inherited PCa. It corroborates the genetic basis for familial PCa, whereas all previous linkage studies of families with hereditary PCa provided inconsistent results. To date, only genomewide association studies had led to the identification of single-nucleotide polymorphisms, but they could account for only an estimated one-quarter of familial risk [1]. With a carrier rate 20 times higher in men with PCa than in men without PCa, the G84E mutation prompts exploration of what appears as a rare but strong pathway of prostate carcinogenesis, even in more common sporadic cases.

Far from leading to an additional expensive clinical test, this pivotal discovery of the first genetic mutation of PCa is rather encouraging for investigation of large genomic intervals with the new-generation sequencing technologies. The search for other genetic variants should interest the genomic regions associated with elevations in the risk of PCa after linkage analysis [2]. The breast cancer 1, early onset (BRCA1) and breast cancer 2, early onset (BRCA2) genes should also be investigated in populations with early-onset and familial PCa to rule on the controversies about their role in prostate carcinogenesis [3,4].

Conflicts of interest: The authors have nothing to disclose.

References

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Thomas Bessede, Jean-Jacques Patard*
Urology Department, Paris-South University Hospital of Bicetre,
78 rue du General Leclerc, 94270 Le Kremlin-Bicetre, France

*Corresponding author.

E-mail address: jean-jacques.patard@bct.aphp.fr (J.-J. Patard)

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Re: Phase III Study of Molecularly Targeted Adjuvant Therapy in Locally Advanced Urothelial Cancer of the Bladder Based on p53 Status

Stadler WM, Lerner SP, Groshen S, et al

J Clin Oncol 2011;29:3443–9

Experts' summary:

Conventional prognostic indicators for bladder cancer, such as tumor grade, stage, size, variant histopathology, and multifocality, incompletely predict clinical outcome. This trial represents the largest randomized study of adjuvant chemotherapy for bladder cancer and the first study to use methotrexate,