Published in final edited form as:

N Engl J Med. 2012 August 2; 367(5): 480–481. doi:10.1056/NEJMc1205138.

Association of a *HOXB13* Variant with Breast Cancer

Shaheen Alanee, M.D., M.P.H.,

Memorial Sloan-Kettering Cancer Center, New York, NY

Fergus Couch, Ph.D., and

Mayo Clinic, Rochester, MN

Kenneth Offit, M.D., M.P.H.

Memorial Sloan-Kettering Cancer Center, New York, NY

Kenneth Offit: offitk@mskcc.org

TO THE EDITOR

The role of homeobox 13 (*HOXB13*) in hormone-resistant breast cancer has been elucidated only recently. A missense mutation (c.251G→A; p.G84E; rs138213197) in *HOXB13* associated with prostate cancer has been reported.¹ We compared the frequency of rs138213197 C-T heterozygotes in 1170 patients with familial breast cancer (including 293 patients of Ashkenazi Jewish ancestry) and wild-type *BRCA1* and *BRCA2* mutations, 1053 patients with sporadic breast cancer (who were not tested for *BRCA1/2*), 1052 patients with colon cancer, and 1650 healthy controls.

Most patients with breast cancer (70%) were white women with a mean age at diagnosis of 53 years. Germline DNA extracted from blood was available through protocols approved by the institutional review board at the Memorial Sloan-Kettering Cancer Center. Written informed consent was obtained from some patients; in others, this requirement was waived since the analyzed data had no personal identifiers. Genotyping was performed with the use of the TaqMan allelic discrimination assay (Applied Biosystems). We verified the presence of the variant among suspected carriers with the use of Sanger sequencing.

Among 877 patients, 6 women with *BRCA1/2* wild-type, familial breast cancer who were not of Ashkenazi Jewish ancestry were carriers of the rs138213197 variant (0.7%); this rate was seven times as high as the prevalence of the mutation among controls (0.1%) (odds ratio, 5.7; 95% confidence interval, 1.0 to 40.7; exact *P* = 0.02). The mutation carriers were mainly white women who were 38 to 77 years of age at diagnosis, and 4 patients had estrogen-receptor (ER)-positive tumors (Table 1).

We observed 3 heterozygous carriers among the patients with sporadic breast cancer (0.3%), 1 heterozygous carrier among the patients with colon cancer, and no carriers of the mutation in the 293 patients with breast cancer who were of Ashkenazi Jewish ancestry. These findings show an association of this *HOXB13* variant and a risk of *BRCA1/2* wild-type, familial breast cancer. *HOXB13* expression is increased in breast-cancer cells as compared with normal breast epithelium,² and a high ratio of *HOXB13* to interleukin-17B receptor (*IL17BR*) is suggested to signal impaired ER signaling and thus predict resistance to tamoxifen.^{3,4} As evidence of population heterogeneity, the mutation was not seen in

Ashkenazi Jews but was observed in 1 patient with breast cancer who was of black and Native American race. These findings also show a moderate effect size (a risk that was approximately six times as high as the risk among persons without this mutation) for this *HOXB13* variant, which is greater than the risk associated with cell-cycle-check-point kinase (*CHEK2*) mutations or common variants from genomewide association studies (approximately 1.1 to 2.5 times as high as the risk among persons without these genetic changes), but less than the risk of early-onset breast cancer associated with *BRCA1/2* mutations (approximately 10 to 50 times as high as the risk among persons without these mutations). More data are needed to understand the pathogenic role of homeobox genes in breast-cancer susceptibility and the possible clinical usefulness of this *HOXB13* variant.

Acknowledgments

Supported by the Breast Cancer Research Foundation, Niehaus Clinical Cancer Genetics Initiative, Sabin Family Fund, Sidney Kimmel Center for Prostate and Urologic Cancers, and a grant (CA128978) from the National Institutes of Health.

References

1. Ewing CM, Ray AM, Lange EM, et al. Germline mutations in *HOXB13* and prostate-cancer risk. *N Engl J Med*. 2012; 366:141–9. [PubMed: 22236224]
2. Cantile M, Pettinato G, Procino A, Feliciello I, Cindolo L, Cillo C. In vivo expression of the whole HOX gene network in human breast cancer. *Eur J Cancer*. 2003; 39:257–64. [PubMed: 12509959]
3. Ma XJ, Wang Z, Ryan PD, et al. A two-gene expression ratio predicts clinical outcome in breast cancer patients treated with tamoxifen. *Cancer Cell*. 2004; 5:607–16. [PubMed: 15193263]
4. Jerevall PL, Jansson A, Fornander T, Skoog L, Nordenskjold B, Stal O. Predictive relevance of HOXB13 protein expression for tamoxifen benefit in breast cancer. *Breast Cancer Res*. 2010; 12:R53. [PubMed: 20649975]

Table 1

Patient and Tumor Characteristics of Six Heterozygous Carriers of *HOXB13* Mutation (rs138213197) among BRCA-Negative Patients with Non-Ashkenazi Familial Breast Cancer.*

Race	Age at Diagnosis yr	Breast Cancer Histology	Estrogen-Receptor Status
Native American and black	46	Mixed ductal and lobular carcinoma in situ	Unknown
White	38	Ductal	Positive
White	45	Invasive lobular	Positive
White	39	Invasive lobular	Positive
White	46	Unknown	Unknown
Unknown	77	Invasive ductal	Positive

* Race was self-reported.