EUROPEAN UROLOGY 81 (2022) 458–462

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

Platinum Priority – Brief Correspondence

Editorial by Andrew J. Vickers, Aymen Elfiky, Vincent L. Freeman, Mack Roach 3rd on pp. 463–465 of this issue

A Rare Germline HOXB13 Variant Contributes to Risk of Prostate Cancer in Men of African Ancestry

Burcu F. Darst[a,b,*], Raymond Hughley[a], Aaron Pfennig[c], Ujani Hazra[c], Caoqi Fan[a,d], Peggy Wan[a], Xin Sheng[a], Lucy Xia[a], Caroline Andrews[e], Fei Chen[a], Sonja I. Berndt[f], Zsofia Kote-Jarai[g], Koveela Govindasami[g,h], Jeannette T. Bensen[i,j], Sue A. Ingles[a,b], Benjamin A. Rybicki[k], Barbara Nemesure[l], Esther M. John[m], Jay H. Fowke[n], Chad D. Huff[o], Sara S. Strom[o], William B. Isaacs[p], Jong Y. Park[q], Wei Zheng[r], Elaine A. Ostrander[s], Patrick C. Walsh[p], John Carpten[t], Thomas A. Sellers[q], Kosj Yamoah[u], Adam B. Murphy[v], Maureen Sanderson[w], Dana C. Crawford[x], Susan M. Gapstur[y], William S. Bush[x], Melinda C. Aldrich[z], Olivier Cussenot[aa], Gyorgy Petrovics[ab], Jennifer Cullen[ab,ac], Christine Neslund-Dudas[k], Rick A. Kittles[ad], Jianfeng Xu[ae], Mariana C. Stern[a,b], Anand P. Chokkalingam[af], Luc Multigner[ag], Marie-Elise Parent[ah], Florence Menegaux[ai], Geraldine Cancel-Tassin[aa], Adam S. Kibel[aj,ak], Eric A. Klein[al], Phyllis J. Goodman[am], Janet L. Stanford[an,ao], Bettina F. Drake[ap], Jennifer J. Hu[aq], Peter E. Clark[ar], Pascal Blanchet[as], Graham Casey[at], Anselm J.M. Hennis[au,av], Alexander Lubwama[aw], Ian M. Thompson Jr[ax], Robin J. Leach[ay], Susan M. Gundell[a], Loreall Pooler[a], James L. Mohler[j,az], Elizabeth T.H. Fontham[ba], Gary J. Smith[az], Jack A. Taylor[bb,bc], Laurent Brureau[as], William J. Blot[r], Richard Biritwum[bd], Evelyn Tay[bd], Ann Truelove[be], Shelley Niwa[be], Yao Tettey[bd,bf], Rohit Varma[bg], Roberta McKean-Cowdin[a,b], Mina Torres[bg], Mohamed Jalloh[bh], Serigne Magueye Gueye[bh], Lamine Niang[bh], Olufemi Ogunbiyi[bi], Michael Oladimeji Idowu[bj], Olufemi Popoola[bi], Akindele O. Adebiyi[bi], Oseremen I. Aisuodionoe-Shadrach[bk], Maxwell Nwegbu[bk], Ben Adusei[bl], Sunny Mante[bl], Afua Darkwa-Abrahams[bd], Edward D. Yeboah[bd,bf], James E. Mensah[bd], Andrew Anthony Adjei[bd], Halimatou Diop[bm], Michael B. Cook[f], Stephen J. Chanock[f], Stephen Watya[aw,bn], Rosalind A. Eeles[g,h], Charleston W.K. Chiang[a,d], Joseph Lachance[c], Timothy R. Rebbeck[e], David V. Conti[a,b], Christopher A. Haiman[a,b,*]

[a] Center for Genetic Epidemiology, Department of Population and Public Health Sciences, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA; [b] Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, CA, USA; [c] School of Biological Sciences, Georgia Institute of Technology, Atlanta, GA, USA; [d] Department of Quantitative and Computational Biology, University of Southern California, Los Angeles, CA, USA; [e] Harvard TH Chan School of Public Health and Division of Population Sciences, Dana Farber Cancer Institute, Boston, MA, USA; [f] Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institute of Health, Bethesda, MD, USA; [g] The Institute of Cancer Research, Sutton, London, UK; [h] Royal Marsden NHS Foundation Trust, London, UK; [i] Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; [j] Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; [k] Department of Public Health Sciences, Henry Ford Hospital, Detroit, MI, USA; [l] Department of Family, Population and Preventive Medicine, Stony Brook University, Stony Brook, NY, USA; [m] Department of Epidemiology & Population Health and Stanford Cancer Institute, Stanford University School of Medicine, Stanford, CA, USA; [n] Division of Epidemiology, Department of Preventive Medicine, The University of Tennessee Health Science Center, TN, USA; [o] Department of Epidemiology, University of Texas M.D. Anderson Cancer Center, Houston, TX, USA; [p] James Buchanan Brady Urological Institute, Johns Hopkins Hospital and Medical Institution, Baltimore, MD, USA; [q] Department of Cancer Epidemiology, Moffitt Cancer Center & Research Institute, Tampa, FL, USA; [r] Division of Epidemiology, Department of Medicine, Vanderbilt Epidemiology Center, Vanderbilt University School of Medicine, Nashville, TN, USA; [s] Cancer Genetics and Comparative Genomics Branch, National

https://doi.org/10.1016/j.eururo.2021.12.023

Human Genome Research Institute, National Institutes of Health, Bethesda, MD, USA; [t] Department of Translational Genomics, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA; [u] Department of Radiation Oncology and Cancer Epidemiology, Moffitt Cancer Center & Research Institute, Tampa, FL, USA; [v] Department of Urology, Northwestern University, Chicago, IL, USA; [w] Department of Family and Community Medicine, Meharry Medical College, Nashville, TN, USA; [x] Cleveland Institute for Computational Biology, Department of Population and Quantitative Health Sciences, Case Western Reserve University, Cleveland, OH, USA; [y] Epidemiology Research Program, American Cancer Society, Atlanta, GA, USA; [z] Department of Thoracic Surgery, Division of Epidemiology, Vanderbilt University Medical Center, Nashville, TN, USA; [aa] CeRePP & Sorbonne Universite, GRC n° 5, AP-HP, Tenon Hospital, Paris, France; [ab] Center for Prostate Disease Research, Department of Surgery, Uniformed Services University of the Health Sciences, Bethesda, MD, USA; [ac] Department of Population and Quantitative Health Sciences, Case Western Reserve University, Cleveland, OH, USA; [ad] Department of Population Sciences, City of Hope Comprehensive Cancer Center, Duarte, CA, USA; [ae] Program for Personalized Cancer Care and Department of Surgery, NorthShore University HealthSystem, Evanston, IL, USA; [af] School of Public Health, University of California, Berkeley, Berkeley, CA, USA; [ag] Univ Rennes, Inserm, EHESP, Irset (Institut de recherche en santé, environnement et travail) -UMR_S 1085, Rennes, France; [ah] Centre Armand-Frappier Santé Biotechnologie, Institut national de la recherche scientifique, University of Quebec, Laval, Quebec, Canada; [ai] Université Paris-Saclay, Université Paris-Sud, CESP (Center for Research in Epidemiology and Population Health), Inserm, Team Cancer-Environment, Villejuif, France; [aj] Division of Urology, Brigham and Women's Hospital/Dana-Farber Cancer Institute, Boston, MA, USA; [ak] Washington University, St. Louis, MO, USA; [al] Glickman Urological & Kidney Institute, Cleveland Clinic, Cleveland, OH, USA; [am] SWOG Statistical Center, Fred Hutchinson Cancer Research Center, Seattle, WA, USA; [an] Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA, USA; [ao] Department of Epidemiology, School of Public Health, University of Washington, Seattle, WA, USA; [ap] Department of Surgery, Division of Public Health Sciences, Washington University School of Medicine, St. Louis, MO, USA; [aq] Sylvester Comprehensive Cancer Center and Department of Public Health Sciences, University of Miami Miller School of Medicine, Miami, FL, USA; [ar] Atrium Health/Levine Cancer Institute, Charlotte, NC, USA; [as] CHU de Guadeloupe, Univ Antilles, Inserm, EHESP, Irset (Institut de recherche en santé, environnement et travail) -UMR_S 1085, Rennes, France; [at] Center for Public Health Genomics, Department of Public Health Sciences, University of Virginia, Charlottesville, VA, USA; [au] Department of Preventive Medicine, Stony Brook University, Stony Brook, NY, USA; [av] George Alleyne Chronic Disease Research Centre and Faculty of Medical Sciences, The University of the West Indies, Bridgetown, Barbados; [aw] School of Public Health, Makerere University College of Health Sciences, Kampala, Uganda; [ax] CHRISTUS Santa Rosa Health System and The University of Texas Health Science Center, San Antonio, TX, USA; [ay] Department of Cell Systems and Anatomy, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA; [az] Department of Urology, Roswell Park Cancer Institute, Buffalo, NY, USA; [ba] School of Public Health, Louisiana State University Health Sciences Center, New Orleans, LA, USA; [bb] Epigenetic and Stem Cell Biology Laboratory, National Institute of Environmental Health Sciences, Research Triangle Park, NC, USA; [bc] Epidemiology Branch, National Institute of Environmental Health Sciences, Research Triangle Park, NC, USA; [bd] Korle Bu Teaching Hospital, Accra, Ghana; [be] Westat, Rockville, MD, USA; [bf] University of Ghana Medical School, Accra, Ghana; [bg] Southern California Eye Institute, CHA Hollywood Presbyterian Medical Center, Los Angeles, CA, USA; [bh] Hôpital Général Idrissa Pouye, Dakar, Senegal; [bi] College of Medicine, University of Ibadan and University College Hospital, Ibadan, Nigeria; [bj] College of Medicine, University of Ibadan, Ibadan, Nigeria; [bk] College of Health Sciences, University of Abuja, University of Abuja Teaching Hospital and Cancer Science Center, Abuja, Nigeria; [bl] 37 Military Hospital, Accra, Ghana; [bm] Laboratoires Bacteriologie et Virologie, Hôpital Aristide Le Dantec, Dakar, Senegal; [bn] Uro Care, Kampala, Uganda

Article info

Article history:
Accepted December 22, 2021

Associate Editor:
James Catto

Keywords:
African ancestry
Allelic age
Genetics
Health disparities
HOXB13
Prostate cancer
Rare genetic variants

Abstract

A rare African ancestry–specific germline deletion variant in *HOXB13* (X285K, rs77179853) was recently reported in Martinican men with early-onset prostate cancer. Given the role of *HOXB13* germline variation in prostate cancer, we investigated the association between *HOXB13* X285K and prostate cancer risk in a large sample of 22 361 African ancestry men, including 11 688 prostate cancer cases. The risk allele was present only in men of West African ancestry, with an allele frequency in men that ranged from 0.40% in Ghana and 0.31% in Nigeria to 0% in Uganda and South Africa, with a range of frequencies in men with admixed African ancestry from North America and Europe (0–0.26%). *HOXB13* X285K was associated with 2.4-fold increased odds of prostate cancer (95% confidence interval [CI] = 1.5-3.9, $p = 2 \times 10^{-4}$), with greater risk observed for more aggressive and advanced disease (Gleason $\geq$8: odds ratio [OR] = 4.7, 95% CI = 2.3–9.5, $p = 2 \times 10^{-5}$; stage T3/T4: OR = 4.5, 95% CI = 2.0–10.0, $p = 2 \times 10^{-4}$; metastatic disease: OR = 5.1, 95% CI = 1.9–13.7, $p = 0.001$). We estimated that the allele arose in West Africa 1500–4600 yr ago. Further analysis is needed to understand how the *HOXB13* X285K variant impacts the HOXB13 protein and function in the prostate. Understanding who carries this mutation may inform prostate cancer screening in men of West African ancestry.

Patient summary: A rare African ancestry–specific germline deletion in *HOXB13*, found only in men of West African ancestry, was reported to be associated with an increased risk of overall and advanced prostate cancer. Understanding who carries this mutation may help inform screening for prostate cancer in men of West African ancestry.

---

* Corresponding authors. Center for Genetic Epidemiology, Department of Population and Public Health Sciences, Keck School of Medicine, University of Southern California, 1450 Biggy Street, Los Angeles, CA 90033, USA. Tel. +1 323 442 0078 (B.F. Darst); Tel. +1 323 442 7755 (C.A. Haiman).
E-mail addresses: bdarst@usc.edu (B.F. Darst), haiman@usc.edu (C.A. Haiman).

The nonsynonymous rare germline *HOXB13* G84E variant (rs138213197) is a major risk factor for prostate cancer, accounting for $\sim$5% of hereditary prostate cancer in men of European ancestry [1,2]. Rare prostate cancer *HOXB13* risk variants have also been observed in other populations, including missense variants G132E in Japanese men (rs1286034091; allele frequency = 0.04%) [3] and G135E in Chinese men (rs769634543; allele frequency = 0.004%) [4]. Recently, a rare African ancestry–specific germline deletion variant in *HOXB13* (rs77179853, allele frequency = 0.2%), which removes the stop codon (X285K) and elongates the HOXB13 protein, was observed in three Martinican men (French West Indies) with early-onset prostate cancer (allele frequency = 3.2%) [5]. Given the critical role of *HOXB13* germline variation in prostate cancer, we investigated the association between the *HOXB13* X285K variant and prostate cancer risk in a large sample of men of African ancestry.

This investigation included 11 688 prostate cancer cases and 10 673 controls from the African Ancestry Prostate Cancer (AAPC) Consortium, ELLIPSE/PRACTICAL OncoArray Consortium, California/Uganda Prostate Cancer Study, Ghana Prostate Study, and Men of African Descent and Carcinoma of the Prostate (MADCaP) Network (Supplementary Tables 1 and 2). The *HOXB13* X285K variant was not included on genome-wide association studies (GWAS) arrays used in the African ancestry prostate cancer studies and was imputed separately using the Trans-Omics for Precision Medicine (TOPMed) r2 and 1000 Genomes Project (1KGP) phase 3 reference panels; the variant was observed in approximately 126 of 97 256 TOPMed participants and three of 2504 1KGP participants (Supplementary material). We imputed 101 carriers among 22 361 men in the African ancestry studies when using the TOPMed panel (imputation info score range across studies: 0.92–0.97) versus 60 when using 1KGP (imputation info score range across studies: 0.68–0.82; Supplementary Table 3). The carrier concordance between imputation panels was 0% (Supplementary Fig. 1). Confirmatory genotyping of 82 TOPMed imputed carriers, 42 1KGP imputed carriers, and 1431 imputed noncarriers confirmed 81 of 82 TOPMed but none of the 1KGP imputed genotypes (Supplementary Fig. 1 and Supplementary material). Other pathogenic and deleterious variants in *HOXB13* were observed in our African ancestry populations (Supplementary Table 4), but were extremely rare and not able to be imputed with high confidence and tested in the current study.

HOXB13 X285K was present only in men of West African ancestry (Fig. 1 and Supplementary Fig. 2), with an allele frequency ranging from 0% in men from Uganda and South Africa to 0.31% in controls from Nigeria and 0.40% in controls from Ghana (Supplementary Table 5). Allele frequencies ranged from 0% to 0.26% in African ancestry controls from North America, the UK, and France (Supplementary Table 5), likely due to the high degree of European admixture in these populations. Of the 22 361 men, those with greater West African ancestry were found to have larger risk allele frequencies, ranging from 0.05% in cases with 0–20% West African ancestry to 0.90% in cases with 80–100% West African ancestry (Fisher's exact test $p = 2 \times 10^{-4}$; Supplementary Fig. 3 and Supplementary material).

In studies where the variant was observed (10 477 cases and 9688 controls; Supplementary Table 2), the *HOXB13*

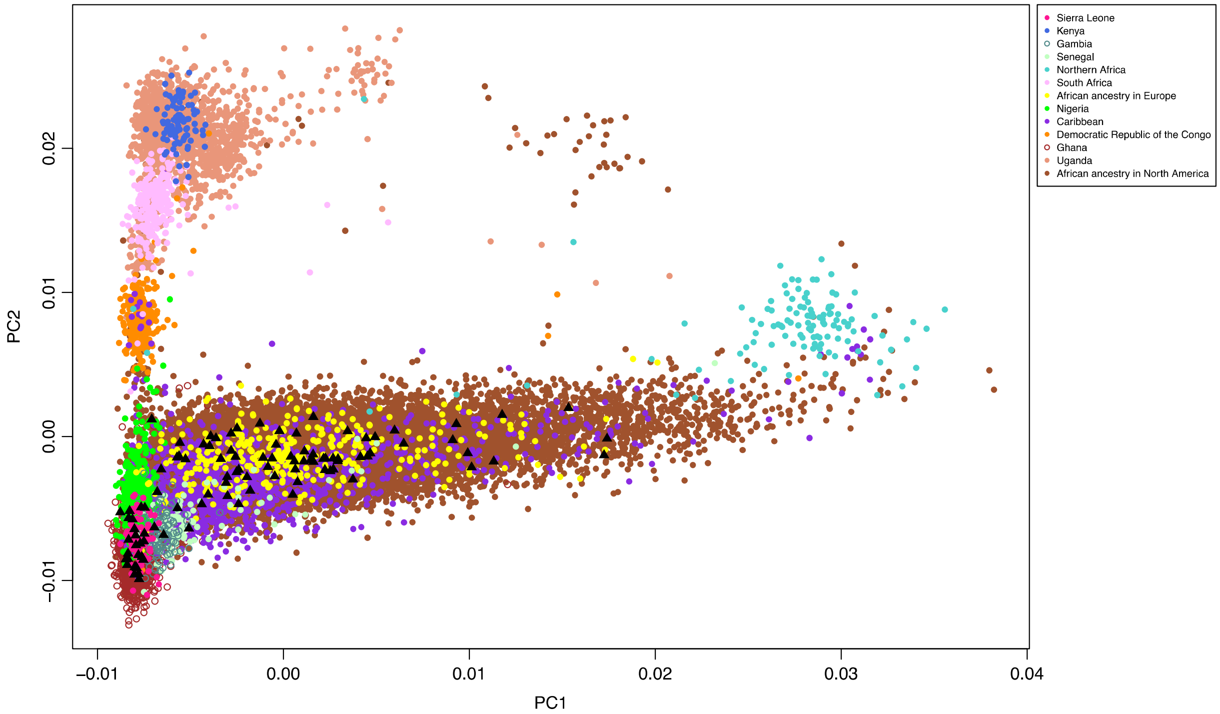

Fig. 1 – Distribution of *HOXB13* rs77179853 by genetic ancestry comparing principal components 1 and 2 calculated in our sample of 22 361 men of African ancestry. Men carrying the rs77179853 delA risk allele are highlighted by black triangles.

Table 1 – Association of *HOXB13* germline variant rs77179853 with prostate cancer risk and disease aggressiveness.[a]

Group	*n*	Carriers, *n*	Risk allele frequency (%)	Carrier frequency (%)	OR (95% CI)	*p* value
Overall prostate cancer						
Controls (reference)	9688	28	0.14	0.29	–	–
Cases	10 477	73	0.35	0.70	2.42 (1.52–3.87)	2×10^{-4}
Men of African ancestry from North America						
Controls (reference)	8766	21	0.12	0.24	–	–
Cases	9192	44	0.24	0.48	1.98 (1.16–3.38)	0.01
Men of African ancestry from West African countries (Ghana, Nigeria, and Senegal)						
Controls (reference)	922	7	0.38	0.76	–	–
Cases	920	22	1.20	2.39	3.99 (1.46–10.9)	0.01
Disease aggressiveness						
Controls (reference)	9180	28	0.15	0.31	–	–
Gleason ≤6 tumors	3319	19	0.29	0.57	2.58 (1.28–5.18)	0.01
Gleason 7 tumors	3056	22	0.36	0.72	2.28 (1.22–4.24)	0.01
Gleason ≥8 tumors [b]	1126	19	0.84	1.69	4.65 (2.28–9.47)	2×10^{-5}
Controls (reference)	8918	28	0.16	0.31	–	–
Stage T1/T2	4784	33	0.34	0.69	2.30 (1.28–4.14)	0.01
Stage T3/T4	959	14	0.73	1.46	4.48 (2.01–9.98)	2×10^{-4}
Controls (reference)	6526	20	0.15	0.31	–	–
Metastatic or PSA ≥100 ng/ml	511	11	1.08	2.15	5.08 (1.88–13.7)	0.001
Controls (reference)	9688	28	0.14	0.29	–	–
Cases with low-risk disease [c,d]	2795	12	0.21	0.43	1.84 (0.87–3.88)	0.11
Cases with intermediate-risk disease [c,d]	2721	12	0.22	0.44	1.51 (0.73–3.15)	0.27
Cases with high-risk disease [d]	3082	33	0.54	1.07	3.09 (1.75–5.45)	1×10^{-4}

CI = confidence interval; OR = odds ratio; PSA = prostate-specific antigen; RAF = risk allele frequency.

[a] Analyses were limited to studies that carried the variant (see Supplementary Table 2).

[b] Compared with 8329 controls (25 carriers, RAF = 0.15%) as the CA UG study did not have Gleason ≥8 tumor case carriers.

[c] Compared with 9400 controls (27 carriers, RAF = 0.14%) as MADCaP did not have low- or intermediate-risk case carriers.

[d] Low risk disease: Gleason <7, stage T1/T2, and PSA <10 ng/ml; intermediate-risk disease: Gleason = 7, stage T1/T2, and PSA = 10–20 ng/ml; high-risk disease: Gleason 8–10, stage T3/T4, PSA >20 ng/ml, metastatic disease, or died of prostate cancer.

X285K variant was significantly associated with 2.4-fold increased odds of prostate cancer (95% confidence interval [CI] = 1.5–3.9, $p = 2 \times 10^{-4}$; allele frequency in cases = 0.35% and controls = 0.14%; Table 1 and Supplementary material). The allele frequency was more common in cases with higher Gleason scores (0.29% in men with Gleason ≤6 tumors [odds ratio {OR} = 2.6, 95% CI = 1.3–5.2, $p = 0.01$], 0.36% in men with Gleason 7 tumors [OR = 2.3, 95% CI = 1.2–4.2, $p = 0.01$], and 0.84% in men with Gleason ≥8 tumors [OR = 4.7, 95% CI = 2.3–9.5, $p = 2 \times 10^{-5}$]), in cases diagnosed with higher-stage disease (0.34% in men with stage T1/T2 disease [OR = 2.3, 95% CI = 1.3–4.1, $p = 0.01$] and 0.73% in men with stage T3/T4 disease [OR = 4.5, 95% CI = 2.0–10.0, $p = 2 \times 10^{-4}$]), and in cases with metastatic (or prostate-specific antigen ≥100 ng/ml) disease (1.08% [OR = 5.1, 95% CI = 1.9–13.7, $p = 0.001$]; Table 1 and Supplementary Table 6).

The absolute risk of prostate cancer was 15.9% (95% CI = 15.9–16.0%) in noncarriers and 32.9% (95% CI = 22.0–44.6%) in carriers by age 85 yr (Supplementary Fig. 4). We did not observe associations between the variant and age at diagnosis (Supplementary Tables 7 and 8), family history of prostate cancer (Supplementary Table 9), or prostate-specific antigen levels (Supplementary Table 10).

We estimated that the *HOXB13* X285K variant arose approximately 1500–4600 yr ago (refer to Supplementary Fig. 5 and Supplementary material for details on allelic age estimates based on two complementary approaches) and likely occurred after the Bantu migration from Western to Southern and Eastern Africa [6], which may explain why it is found only in men of West African ancestry. These findings, together with the established prostate cancer susceptibility G84E founder mutation that is more prevalent in Scandinavian populations [7] and the East Asian–specific G132E and G135E mutations [3,4], underscore the importance of ancestry-specific germline prostate cancer risk variants in the *HOXB13* gene.

The *HOXB13* X285K variant adds to growing evidence of regional differences in Africa for prostate cancer risk variants [8,9] and provides the first evidence of a genetic factor that is limited to specific African ancestry populations, although studies in other populations are needed to better understand the distribution of this variant in Africa. This investigation also demonstrates the importance and necessity of building diverse reference panels to facilitate the discovery of rare ancestry-specific risk variants and the need for larger sequencing studies in prostate cancer. At an exome-wide significance threshold of $p < 5 \times 10^{-7}$, 18 000 cases and 18 000 controls would be needed to detect an OR of 2.4 for an allele frequency of 0.14% (eg, *HOXB13* X285K) with 90% power. The X285K stop codon is predicted to result in a 34% elongation of the HOXB13 protein, extending it by 96 amino acids [10]. Further studies are needed to understand how the *HOXB13* X285K variant impacts the function of this homeobox transcription factor in the prostate. Understanding who carries this mutation may help inform screening for prostate cancer in men of West African ancestry.

Author contributions: Burcu F. Darst had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Haiman.

Acquisition of data: Wan, Sheng, Xia, Andrews, Berndt, Kote-Jarai, Govindasami, Bensen, Ingles, Rybicki, Nemesure, John, Fowke, Huff, Strom, Isaacs, Park, Zheng, Ostrander, Walsh, Carpten, Sellers, Yamoah, Murphy, Maureen Sanderson, Crawford, Gapstur, Bush, Aldrich, Cussenot, Petrovics, Cullen, Neslund-Dudas, Kittles, Xu, Stern, Chokkalingam, Multigner, Parent, Menegaux, Cancel-Tassin, Kibel, Klein, Goodman, Stanford, Drake, Hu, Clark, Blanchet, Casey, Hennis, Lubwama, Thompson Jr, Leach, Gundell, Pooler, Mohler, Fontham, Smith, Taylor, Brureau, Blot, Biritwum, Tay, Truelove, Niwa, Tettey, Varma, McKean-Cowdin, Torres, Jalloh, Gueye, Niang, Ogunbiyi, Idowu, Popoola, Adebiyi, Aisuodionoe-Shadrach, Nwegbu, Adusei, Mante, Darkwa-Abrahams, Yeboah, Mensah, Adjei, Diop, Cook, Chanock, Watya, Eeles, Lachance, Rebbeck, Conti, Haiman.

Analysis and interpretation of data: Darst, Hughley, Pfennig, Hazra, Fan, Wan, Sheng, Xia, Chen, Chiang, Lachance, Conti, Haiman.

Drafting of the manuscript: Darst, Pfennig, Hazra, Fan, Chiang, Lachance, Conti, Haiman.

Critical revision of the manuscript for important intellectual content: Darst, Hughley, Sheng, Multigner, Crawford, Lachance, Conti, Haiman.

Statistical analysis: Darst, Hughley, Pfennig, Hazra, Fan, Wan, Sheng, Xia.

Obtaining funding: Conti, Haiman.

Administrative, technical, or material support: Wan, Sheng, Xia, Gundell, Pooler.

Supervision: Haiman.

Other: None.

Financial disclosures: Burcu F. Darst certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Funding/Support and role of the sponsor: This work was supported by the National Cancer Institute at the National Institutes of Health, grants U19 CA148537, U19 CA214253, R01 CA165862, K99CA246063 and the Prostate Cancer Foundation, grant 20CHAS03. Dr. Burcu F. Darst was supported in part by an award from the Achievement Rewards for College Scientists Foundation Los Angeles Founder Chapter.

Acknowledgments: A full listing of acknowledgments is detailed in the Supplementary material.

Appendix A: Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.eururo.2021.12.023.

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.
[2] Xu J, Lange EM, Lu L, Zheng SL, 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.
[3] Momozawa Y, Iwasaki Y, Hirata M, et al. Germline pathogenic variants in 7636 Japanese patients with prostate cancer and 12 366 controls. J Natl Cancer Inst 2020;112:369–76.
[4] 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;73:169–75.
[5] Marlin R, Creoff M, Merle S, et al. Mutation HOXB13 c.853delT in Martinican prostate cancer patients. Prostate 2020;80:463–70.
[6] Choudhury A, Aron S, Botigue LR, et al. High-depth African genomes inform human migration and health. Nature 2020;586:741–8.
[7] Karlsson R, Aly M, Clements M, et al. A population-based assessment of germline HOXB13 G84E mutation and prostate cancer risk. Eur Urol 2014;65:169–76.
[8] Lachance J, Berens AJ, Hansen MEB, Teng AK, Tishkoff SA, Rebbeck TR. Genetic hitchhiking and population bottlenecks contribute to prostate cancer disparities in men of African descent. Cancer Res 2018;78:2432–43.
[9] Harlemon M, Ajayi O, Kachambwa P, et al. A custom genotyping array reveals population-level heterogeneity for the genetic risks of prostate cancer and other cancers in Africa. Cancer Res 2020;80:2956–66.
[10] Akbari MR, Trachtenberg J, Lee J, et al. Association between germline HOXB13 G84E mutation and risk of prostate cancer. J Natl Cancer Inst 2012;104:1260–2.