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Germline *HOXB13* mutations p.G84E and p.R217C do not confer an increased breast cancer risk

Jingjing Liu^{1,2}, Wendy J. C. Prager - van der Smissen¹, J. Margriet Collée³, Manjeet K. Bolla⁴, Qin Wang⁴, Kyriaki Michailidou^{4,5,6}, Joe Dennis⁴, Thomas U. Ahearn⁷, Kristiina Aittomäki⁸, Christine B. Ambrosone⁹, Irene L. Andrulis^{10,11}, Hoda Anton-Culver¹², Natalia N. Antonenkova¹³, Volker Arndt¹⁴, Norbert Arnold^{15,16}, Kristan J. Aronson¹⁷, Annelie Augustinsson¹⁸, Päivi Auvinen^{19,20,21}, Heiko Becher^{22,23}, Matthias W. Beckmann²⁴, Sabine Behrens²⁵, Marina Bermisheva²⁶, Leslie Bernstein²⁷, Natalia V. Bogdanova^{13,28,29}, Nadja Bogdanova-Markov³⁰, Stig E. Bojesen^{31,32,33}, Hiltrud Brauch^{34,35,36}, Hermann Brenner^{14,36,37}, Ignacio Briceno^{38,39}, Sara Y. Brucker⁴⁰, Thomas Brüning⁴¹, Barbara Burwinkel^{42,43}, Qiuyin Cai⁴⁴, Hui Cai⁴⁴, Daniele Campa^{25,45}, Federico Canzian⁴⁶, Jose E. Castela⁴⁷, Jenny Chang-Claude^{25,48}, Stephen J. Chanock⁷, Ji-Yeob Choi^{49,50}, Melissa Christiaens⁵¹, Christine L. Clarke⁵², NBCS Collaborators*, Fergus J. Couch⁶³, Kamila Czene⁶⁴, Mary B. Daly⁶⁵, Peter Devilee^{66,67}, Isabel dos-Santos-Silva⁶⁸, Miriam Dwek⁶⁹, Diana M. Eccles⁷⁰, A. Heather Eliassen^{71,72}, Peter A. Fasching^{24,73}, Jonine Figueroa^{7,74,75}, Henrik Flyger⁷⁶, Lin Fritschy⁷⁷, Manuela Gago-Dominguez^{78,79}, Susan M. Gapstur⁸⁰, Montserrat Garcia-Closas⁷, José A. García-Sáenz⁸¹, Mia M. Gaudet⁸⁰, Graham G. Giles^{82,83,84}, Mark S. Goldberg^{85,86}, David E. Goldgar⁸⁷, Pascal Guénel⁸⁸, Christopher A. Haiman⁸⁹, Niclas Håkansson⁹⁰, Per Hall^{64,91}, Patricia A. Harrington⁹², Steven N. Hart⁹³, Mikael Hartman^{94,95}, Peter Hillemanns²⁹, John L. Hopper⁸³, Ming-Feng Hou⁹⁶, David J. Hunter^{72,97,98}, Dezheng Huo⁹⁹, ABCTB Investigators*, Hidemi Ito^{100,101}, Motoki Iwasaki¹⁰², Milena Jakimovska¹⁰³, Anna Jakubowska^{104,105}, Esther M. John¹⁰⁶, Rudolf Kaaks²⁵, Daehee Kang^{49,50,107}, Renske Keeman¹⁰⁸, Elza Khusnutdinova^{26,109}, Sung-Won Kim¹¹⁰, Peter Kraft^{72,97}, Vessela N. Kristensen¹¹¹, Allison W. Kurian^{106,112}, Loïc Le Marchand¹¹³, Jingmei Li¹¹⁴, Annika Lindblom^{115,116}, Artitaya Lophatananon¹¹⁷, Robert N. Luben¹¹⁸, Jan Lubinski¹⁰⁴, Arto Mannermaa^{21,119,120}, Mehdi Manoochehri¹²¹, Siranoush Manoukian¹²², Sara Margolin^{91,123}, Shivaani Mariapun¹²⁴, Keitaro Matsuo^{100,101}, Tabea Maurer⁴⁸, Dimitrios Mavroudis¹²⁵, Alfons Meindl¹²⁶, Usha Menon¹²⁷, Roger L. Milne^{82,83,84}, Kenneth Muir¹¹⁷, Anna Marie Mulligan^{128,129}, Susan L. Neuhausen²⁷, Heli Nevanlinna¹³⁰, Kenneth Offit^{131,132}, Olufunmilayo I. Olopade⁹⁹, Janet E. Olson⁹³, Håkan Olsson¹⁸, Nick Orr^{133,134}, Sue K. Park^{49,50,107}, Paolo Peterlongo¹³⁵, Julian Peto⁶⁸, Dijana Plaseska-Karanfilska¹⁰³, Nadege Presneau⁶⁹, Brigitte Rack¹³⁶, Rohini Rau-Murthy¹³², Gad Rennert¹³⁷, Hedy S. Rennert¹³⁷, Valerie Rhenius⁹², Atocha Romero¹³⁸, Matthias Ruebner¹³⁹, Emmanouil Saloustros¹⁴⁰, Rita K. Schmutzler^{141,142,143}, Andreas Schneeweiss^{43,144}, Christopher Scott⁹³, Mitul Shah⁹², Chen-Yang Shen^{145,146}, Xiao-Ou Shu⁴⁴, Jacques Simard¹⁴⁷, Christof Sohn¹⁴⁴, Melissa C. Southey^{82,84,148}, John J. Spinelli^{149,150}, Rulla M. Tamimi^{71,72,97}, William J. Tapper⁷⁰, Soo H. Teo^{151,152}, Mary Beth Terry¹⁵³, Diana Torres^{38,121}, Thérèse Truong⁸⁸, Michael Untch¹⁵⁴, Celine M. Vachon¹⁵⁵, Christi J. van Asperen¹⁵⁶, Alicja Wolk^{90,157}, Taiki Yamaji¹⁰², Wei Zheng⁴⁴, Argyrios Ziogas¹², Elad Ziv¹⁵⁸, Gabriela Torres-Mejía¹⁵⁹, Thilo Dörk²⁹, Anthony J. Swerdlow^{160,161}, Ute Hamann¹²¹, Marjanka K. Schmidt^{108,162}, Alison M. Dunning⁹², Paul D. P. Pharoah^{4,92}, Douglas F. Easton^{4,92}, Maartje J. Hoening¹, John W. M. Martens¹ & Antoinette Hollestelle¹✉

¹Department of Medical Oncology, Family Cancer Clinic, Erasmus MC Cancer Institute, Rotterdam, The Netherlands. ²Institute of Medical and Pharmaceutical Sciences, Zhengzhou University, Zhengzhou, China. ³Department of Clinical Genetics, Erasmus University Medical Center, Rotterdam, The Netherlands. ⁴Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK. ⁵Biostatistics Unit, The Cyprus Institute of Neurology & Genetics, Nicosia, Cyprus. ⁶Cyprus School of Molecular Medicine, The Cyprus Institute of Neurology & Genetics, Nicosia, Cyprus. ⁷Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, MD, USA. ⁸Department of Clinical Genetics, Helsinki University Hospital, University of Helsinki, Helsinki, Finland. ⁹Roswell Park Cancer Institute, Buffalo, NY, USA. ¹⁰Fred A. Litwin Center for Cancer Genetics, Lunenfeld-Tanenbaum Research Institute of Mount Sinai Hospital, Toronto, ON, Canada. ¹¹Department of Molecular Genetics, University of Toronto, Toronto, ON, Canada. ¹²Department of Epidemiology, Genetic Epidemiology Research Institute, University of California Irvine, Irvine, CA, USA. ¹³N.N. Alexandrov Research Institute of Oncology and Medical Radiology, Minsk, Belarus. ¹⁴Division of Clinical Epidemiology and Aging Research, German Cancer Research Center (DKFZ), Heidelberg, Germany. ¹⁵Department of Gynaecology and Obstetrics, University Hospital of Schleswig-Holstein, Campus Kiel, Christian-Albrechts University Kiel, Kiel, Germany. ¹⁶Institute of Clinical Molecular Biology, University Hospital of Schleswig-Holstein, Campus Kiel, Christian-Albrechts University Kiel, Kiel, Germany. ¹⁷Department of Public Health Sciences, and Cancer Research Institute, Queen's University, Kingston, ON, Canada. ¹⁸Department of Cancer Epidemiology, Clinical Sciences, Lund University, Lund, Sweden. ¹⁹Cancer Center, Kuopio University Hospital, Kuopio, Finland. ²⁰Institute of Clinical Medicine, Oncology, University of Eastern Finland, Kuopio, Finland. ²¹Translational Cancer Research Area, University of Eastern Finland, Kuopio, Finland. ²²Institute of Medical Biometry and Epidemiology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany. ²³Institute of Biometry and Clinical Epidemiology, Charité – Universitätsmedizin Berlin, Berlin, Germany. ²⁴Department of Gynecology and Obstetrics, Comprehensive Cancer Center ER-EMN, University Hospital Erlangen, Friedrich-Alexander-University Erlangen-Nuremberg, Erlangen, Germany. ²⁵Division of Cancer Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany. ²⁶Institute of Biochemistry and Genetics, Ufa Federal Research Centre of the Russian Academy of Sciences, Ufa, Russia. ²⁷Department of Population Sciences, Beckman Research Institute of City of Hope, Duarte, CA, USA. ²⁸Department of Radiation Oncology, Hannover Medical School, Hannover, Germany. ²⁹Gynaecology Research Unit, Hannover Medical School, Hannover, Germany. ³⁰Institute of Human Genetics, University of Münster, Münster, Germany. ³¹Copenhagen General Population Study, Herlev and Gentofte Hospital, Copenhagen University Hospital, Herlev, Denmark. ³²Department of Clinical Biochemistry, Herlev and Gentofte Hospital, Copenhagen University Hospital, Herlev, Denmark. ³³Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark. ³⁴Dr. Margarete Fischer-Bosch-Institute of Clinical Pharmacology, Stuttgart, Germany. ³⁵iFIT-Cluster of Excellence, University of Tübingen, Tübingen, Germany. ³⁶German Cancer Consortium (DKTK), German Cancer Research Center (DKFZ), Partner Site Tübingen, Tübingen, Germany. ³⁷Division of Preventive Oncology, German Cancer Research Center (DKFZ) and National Center for Tumor Diseases (NCT), Heidelberg, Germany. ³⁸Institute of Human Genetics, Pontificia Universidad Javeriana, Bogota, Colombia. ³⁹Medical Faculty, Universidad de La Sabana, Bogota, Colombia. ⁴⁰Department of Gynecology and Obstetrics, University of Tübingen, Tübingen, Germany. ⁴¹Institute for Prevention and Occupational Medicine of the German Social Accident Insurance, Institute of the Ruhr University Bochum (IPA), Bochum, Germany. ⁴²Molecular Epidemiology Group, C080, German Cancer Research Center (DKFZ), Heidelberg, Germany. ⁴³Molecular Biology of Breast Cancer, University Womens Clinic Heidelberg, University of Heidelberg, Heidelberg, Germany. ⁴⁴Division of Epidemiology, Department of Medicine, Vanderbilt Epidemiology Center, Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Nashville, TN, USA. ⁴⁵Department of Biology, University of Pisa, Pisa, Italy. ⁴⁶Genomic Epidemiology Group, German Cancer Research Center (DKFZ), Heidelberg, Germany. ⁴⁷Oncology and Genetics Unit, Instituto de Investigación Sanitaria Galicia Sur (IISGS), Xerencia de Xestión Integrada de Vigo-SERGAS, Vigo, Spain. ⁴⁸Cancer Epidemiology Group, University Cancer Center Hamburg (UCCH), University Medical Center Hamburg-Eppendorf, Hamburg, Germany. ⁴⁹Department of Biomedical Sciences, Seoul National University Graduate School, Seoul, Korea. ⁵⁰Cancer Research Institute, Seoul National University, Seoul, Korea. ⁵¹Leuven Multidisciplinary Breast Center, Department of Oncology, Leuven Cancer Institute, University Hospitals Leuven, Leuven, Belgium. ⁵²Westmead Institute for Medical Research, University of Sydney, Sydney, New South Wales, Australia. ⁵³Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA. ⁵⁴Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden. ⁵⁵Department of Clinical Genetics, Fox Chase Cancer Center, Philadelphia, PA, USA. ⁵⁶Department of Pathology, Leiden University Medical Center, Leiden, The Netherlands. ⁵⁷Department of Human Genetics, Leiden University Medical Center, Leiden, The Netherlands. ⁵⁸Department of Non-Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK. ⁵⁹School of Life Sciences, University of Westminster, London, UK. ⁶⁰Faculty of Medicine, University of Southampton, Southampton, UK. ⁶¹Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA. ⁶²Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA. ⁶³David Geffen School of Medicine, Department of Medicine Division of Hematology and Oncology, University of California at Los Angeles, Los Angeles, CA, USA. ⁶⁴Usher Institute of Population Health Sciences and Informatics, The University of Edinburgh, Edinburgh, UK. ⁶⁵Cancer Research UK Edinburgh Centre, The University of Edinburgh, Edinburgh, UK. ⁶⁶Department of Breast Surgery, Herlev and Gentofte Hospital, Copenhagen University Hospital, Herlev, Denmark. ⁶⁷School of Public Health, Curtin University, Perth, Western Australia, Australia. ⁶⁸Genomic Medicine Group, Galician Foundation of Genomic Medicine, Instituto de Investigación Sanitaria de Santiago de Compostela (IDIS), Complejo Hospitalario Universitario de Santiago, SERGAS, Santiago de Compostela, Spain. ⁶⁹Moore's Cancer Center, University of California San Diego, La Jolla, CA, USA. ⁷⁰Behavioral and Epidemiology Research Group, American Cancer Society, Atlanta, GA, USA. ⁷¹Medical Oncology Department, Hospital Clínico San Carlos, Instituto de Investigación Sanitaria San Carlos (IdISSC), Centro Investigación Biomédica en Red de Cáncer (CIBERONC), Madrid, Spain. ⁷²Cancer Epidemiology Division, Cancer

Council Victoria, Melbourne, Victoria, Australia. ⁸³Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne, Melbourne, Victoria, Australia. ⁸⁴Precision Medicine, School of Clinical Sciences at Monash Health, Monash University, Clayton, Victoria, Australia. ⁸⁵Department of Medicine, McGill University, Montréal, QC, Canada. ⁸⁶Division of Clinical Epidemiology, Royal Victoria Hospital, McGill University, Montréal, QC, Canada. ⁸⁷Department of Dermatology, Huntsman Cancer Institute, University of Utah School of Medicine, Salt Lake City, UT, USA. ⁸⁸Cancer & Environment Group, Center for Research in Epidemiology and Population Health (CESP), INSERM, University Paris-Sud, University Paris-Saclay, Villejuif, France. ⁸⁹Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA. ⁹⁰Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden. ⁹¹Department of Oncology, Södersjukhuset, Stockholm, Sweden. ⁹²Centre for Cancer Genetic Epidemiology, Department of Oncology, University of Cambridge, Cambridge, UK. ⁹³Department of Health Sciences Research, Mayo Clinic, Rochester, MN, USA. ⁹⁴Saw Swee Hock School of Public Health, National University of Singapore and National University Health System, Singapore, Singapore. ⁹⁵Department of Surgery, National University Health System, Singapore, Singapore. ⁹⁶Department of Surgery, Kaohsiung Municipal Hsiao-Kang Hospital, Kaohsiung, Taiwan. ⁹⁷Program in Genetic Epidemiology and Statistical Genetics, Harvard T.H. Chan School of Public Health, Boston, MA, USA. ⁹⁸Nuffield Department of Population Health, University of Oxford, Oxford, UK. ⁹⁹Center for Clinical Cancer Genetics, The University of Chicago, Chicago, IL, USA. ¹⁰⁰Division of Cancer Epidemiology and Prevention, Aichi Cancer Center Research Institute, Nagoya, Japan. ¹⁰¹Division of Cancer Epidemiology, Nagoya University Graduate School of Medicine, Nagoya, Japan. ¹⁰²Division of Epidemiology, Center for Public Health Sciences, National Cancer Center, Tokyo, Japan. ¹⁰³Research Centre for Genetic Engineering and Biotechnology 'Georgi D. Efremov', MASA, Skopje, Republic of North Macedonia. ¹⁰⁴Department of Genetics and Pathology, Pomeranian Medical University, Szczecin, Poland. ¹⁰⁵Independent Laboratory of Molecular Biology and Genetic Diagnostics, Pomeranian Medical University, Szczecin, Poland. ¹⁰⁶Department of Medicine, Division of Oncology, Stanford Cancer Institute, Stanford University School of Medicine, Stanford, CA, USA. ¹⁰⁷Department of Preventive Medicine, Seoul National University College of Medicine, Seoul, Korea. ¹⁰⁸Division of Molecular Pathology, The Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands. ¹⁰⁹Saint Petersburg State University, Saint-Petersburg, Russia. ¹¹⁰Department of Surgery, Daerim Saint Mary's Hospital, Seoul, Korea. ¹¹¹Department of Medical Genetics, Oslo University Hospital and University of Oslo, Oslo, Norway. ¹¹²Department of Health Research and Policy, Stanford University School of Medicine, Stanford, CA, USA. ¹¹³Epidemiology Program, University of Hawaii Cancer Center, Honolulu, HI, USA. ¹¹⁴Human Genetics Division, Genome Institute of Singapore, Singapore, Singapore. ¹¹⁵Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden. ¹¹⁶Department of Clinical Genetics, Karolinska University Hospital, Stockholm, Sweden. ¹¹⁷Division of Population Health, Health Services Research and Primary Care, School of Health Sciences, Faculty of Biology, Medicine and Health, The University of Manchester, Manchester, UK. ¹¹⁸Clinical Gerontology, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK. ¹¹⁹Institute of Clinical Medicine, Pathology and Forensic Medicine, University of Eastern Finland, Kuopio, Finland. ¹²⁰Imaging Center, Department of Clinical Pathology, Kuopio University Hospital, Kuopio, Finland. ¹²¹Molecular Genetics of Breast Cancer, German Cancer Research Center (DKFZ), Heidelberg, Germany. ¹²²Unit of Medical Genetics, Department of Medical Oncology and Hematology, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milan, Italy. ¹²³Department of Clinical Science and Education, Södersjukhuset, Karolinska Institutet, Stockholm, Sweden. ¹²⁴Cancer Research Malaysia, Subang Jaya, Selangor, Malaysia. ¹²⁵Department of Medical Oncology, University Hospital of Heraklion, Heraklion, Greece. ¹²⁶Department of Gynecology and Obstetrics, University of Munich, Campus Großhadern, Munich, Germany. ¹²⁷MRC Clinical Trials Unit at UCL, Institute of Clinical Trials & Methodology, University College London, London, UK. ¹²⁸Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, ON, Canada. ¹²⁹Laboratory Medicine Program, University Health Network, Toronto, ON, Canada. ¹³⁰Department of Obstetrics and Gynecology, Helsinki University Hospital, University of Helsinki, Helsinki, Finland. ¹³¹Clinical Genetics Research Lab, Department of Cancer Biology and Genetics, Memorial Sloan Kettering Cancer Center, New York, NY, USA. ¹³²Clinical Genetics Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA. ¹³³The Breast Cancer Now Toby Robins Research Centre, The Institute of Cancer Research, London, UK. ¹³⁴Centre for Cancer Research and Cell Biology, Queen's University Belfast, Belfast, Ireland, UK. ¹³⁵Genome Diagnostics Program, IFOM - the FIRC Institute for Molecular Oncology, Milan, Italy. ¹³⁶Department of Gynaecology and Obstetrics, University Hospital Ulm, Ulm, Germany. ¹³⁷Clalit National Cancer Control Center, Carmel Medical Center and Technion Faculty of Medicine, Haifa, Israel. ¹³⁸Medical Oncology Department, Hospital Universitario Puerta de Hierro, Madrid, Spain. ¹³⁹Department of Gynaecology and Obstetrics, University Hospital Erlangen, Friedrich-Alexander University Erlangen-Nuremberg, Comprehensive Cancer Center Erlangen-EMN, Erlangen, Germany. ¹⁴⁰Department of Oncology, University Hospital of Larissa, Larissa, Greece. ¹⁴¹Center for Familial Breast and Ovarian Cancer, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany. ¹⁴²Center for Integrated Oncology (CIO), Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany. ¹⁴³Center for Molecular Medicine Cologne (CMMC), Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany. ¹⁴⁴National Center for Tumor Diseases, University Hospital and German Cancer Research Center, Heidelberg, Germany. ¹⁴⁵Institute of Biomedical Sciences, Academia Sinica, Taipei, Taiwan. ¹⁴⁶School of Public Health, China Medical University, Taichung, Taiwan. ¹⁴⁷Genomics Center, Centre Hospitalier Universitaire de Québec – Université Laval Research Center, Québec City, QC, Canada. ¹⁴⁸Department of Clinical Pathology, The University of Melbourne, Melbourne, Victoria, Australia. ¹⁴⁹Population Oncology, BC Cancer, Vancouver, BC, Canada. ¹⁵⁰School of Population and Public Health, University of British Columbia, Vancouver, BC, Canada. ¹⁵¹Breast Cancer Research Programme, Cancer Research Malaysia, Subang Jaya, Selangor, Malaysia. ¹⁵²Department of Surgery, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia. ¹⁵³Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY, USA. ¹⁵⁴Department of Gynecology and Obstetrics, Helios Clinics Berlin-Buch, Berlin, Germany. ¹⁵⁵Department of Health Science Research,

Division of Epidemiology, Mayo Clinic, Rochester, MN, USA. ¹⁵⁶Department of Clinical Genetics, Leiden University Medical Center, Leiden, The Netherlands. ¹⁵⁷Department of Surgical Sciences, Uppsala University, Uppsala, Sweden. ¹⁵⁸Department of Medicine, Institute for Human Genetics, UCSF Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA, USA. ¹⁵⁹Center for Population Health Research, National Institute of Public Health, Cuernavaca, Morelos, Mexico. ¹⁶⁰Division of Genetics and Epidemiology, The Institute of Cancer Research, London, UK. ¹⁶¹Division of Breast Cancer Research, The Institute of Cancer Research, London, UK. ¹⁶²Division of Psychosocial Research and Epidemiology, The Netherlands Cancer Institute - Antoni van Leeuwenhoek hospital, Amsterdam, The Netherlands. *Lists of authors and their affiliations appear at the end of the paper. ✉e-mail: a.hollestelle@erasmusmc.nl

In breast cancer, high levels of homeobox protein Hox-B13 (HOXB13) have been associated with disease progression of ER-positive breast cancer patients and resistance to tamoxifen treatment. Since HOXB13 p.G84E is a prostate cancer risk allele, we evaluated the association between HOXB13 germline mutations and breast cancer risk in a previous study consisting of 3,270 familial non-*BRCA1/2* breast cancer cases and 2,327 controls from the Netherlands. Although both recurrent HOXB13 mutations p.G84E and p.R217C were not associated with breast cancer risk, the risk estimation for p.R217C was not very precise. To provide more conclusive evidence regarding the role of HOXB13 in breast cancer susceptibility, we here evaluated the association between HOXB13 mutations and increased breast cancer risk within 81 studies of the international Breast Cancer Association Consortium containing 68,521 invasive breast cancer patients and 54,865 controls. Both HOXB13 p.G84E and p.R217C did not associate with the development of breast cancer in European women, neither in the overall analysis (OR = 1.035, 95% CI = 0.859–1.246, $P = 0.718$ and OR = 0.798, 95% CI = 0.482–1.322, $P = 0.381$ respectively), nor in specific high-risk subgroups or breast cancer subtypes. Thus, although involved in breast cancer progression, HOXB13 is not a material breast cancer susceptibility gene.

Breast cancer is a complex disease and several classes of germline variants have been identified that together explain about half of the total genetic heritability of breast cancer. These include rare germline mutations in high and moderate penetrance breast cancer susceptibility genes *BRCA1*, *BRCA2*, *CDH1*, *PTEN*, *STK11*, *TP53*, *PALB2*, *ATM*, *CHEK2* and *NBN*¹. In addition, genome-wide association studies (GWASs) have identified over 170 common low penetrance alleles each conferring a small increased risk to develop breast cancer^{2,3}. Importantly, the risks these low penetrance alleles confer combine multiplicatively and since these variants are so common in the population women in the top 1% of risk have a 4.4- and 2.8-fold increased risk to develop ER-positive and ER-negative breast cancer, respectively⁴. Still, to identify better those women at risk for developing breast cancer and establish more precise risk estimates, we need to explain the remainder of the genetic heritability of breast cancer.

In this respect, the rare HOXB13 p.G84E germline mutation (*i.e.* NM_006361.6:c.251 G > A; NP_006352.2:p.(G84E); rs138213197:C > T) was found to be associated with an increased risk to develop prostate cancer by linkage analysis and candidate gene sequencing of 200 genes at the 17q21-22 linkage region⁵. Since then, several studies have validated this association and meta-analyses have shown the prostate cancer risk to be 3- to 4-fold increased for male carriers^{6–8}. Moreover, the p.G84E mutation also associated with early-onset prostate cancer, multiple affected relatives and highly aggressive disease^{6,8}. Considering the evidence, there is a strong consensus for including the HOXB13 gene in genetic testing for hereditary prostate cancer⁹.

In recent years, we have also begun to understand the role of HOXB13 in prostate cancer progression. HOXB13 acts as a transcription factor and, together with the androgen receptor (AR) and FOXA1, regulates expression of the *RFX6* gene which encodes a driver of prostate cancer progression. Interestingly, HOXB13 is preferentially recruited to the risk allele of a prostate cancer risk associated SNP, rs339331, located in an enhancer element upstream of *RFX6*, thereby enhancing *RFX6* expression and promoting more aggressive disease¹⁰. Moreover, HOXB13 also pioneers binding of the constitutively active splice variant 7 of the androgen receptor (AR-V7) to open chromatin of castrate-resistant prostate cancer (CRPC) genomes to upregulate target oncogenes¹¹. Importantly, AR-V7 plays an important role in the anti-AR therapy resistance¹².

In breast cancer, HOXB13 also plays an important role in disease progression. A high HOXB13 to *IL17BR* expression ratio was associated with a high risk of recurrence and poor outcome for estrogen receptor (ER)-positive breast cancer patients^{13–15}. Furthermore, high expression of HOXB13 predicted a poor response to tamoxifen therapy by suppressing ER and activating the mTOR pathway via IL6^{16,17}. Interestingly, a significant fraction of breast cancer risk SNPs have been found to alter the affinity of chromatin for pioneer factor FOXA1 with which HOXB13 interacts in prostate cancer cells^{10,18}. To date, several studies have investigated the association between the germline HOXB13 p.G84E mutation and breast cancer risk, however, these have led to contradictory results^{7,19–21}.

In a previous study, we have sequenced the entire coding region of HOXB13 in 1,250 familial non-*BRCA1/2* breast cancer cases and 800 controls. We identified two recurrent HOXB13 mutations in the female Dutch population, the known prostate cancer risk allele p.G84E, but also p.R217C (*i.e.* NM_006361.6:c.649 C > T; NP_006352.2:p.(R217C); rs139475791:G > A). We found that neither p.G84E nor p.R217C were associated with an increased breast cancer risk (OR = 0.81, 95% CI = 0.41–1.59, $P = 0.54$ and OR = 3.57, 95% CI = 0.76–33.57, $P = 0.14$, respectively) in 3,270 familial non-*BRCA1/2* breast cancer patients and 2,327 controls²². Considering the low carrier allele frequency (CAF; 0.09% in controls) and the very wide confidence intervals for the association between p.R217C and breast cancer risk, larger studies are needed to provide more conclusive evidence.

	N Controls	N Cases	CAF (%) Controls	CAF (%) Cases	OR (95% CI)*	P-value*
Overall analysis						
Europeans	44,298	54,731	0.510	0.471	1.03 (0.86–1.24)	0.74
Subgroup analysis						
Age of diagnosis						
< 50 years	44,298	17,641	0.510	0.431	0.99 (0.72–1.35)	0.98
Menopausal status						
Premenopausal	44,298	12,134	0.510	0.503	1.20 (0.88–1.64)	0.24
Family history						
1 st degree relative with BC	41,876	7,582	0.533	0.462	1.04 (0.72–1.51)	0.83
Second BC						
Contralateral BC	38,310	2,144	0.506	0.373	1.00 (0.48–2.10)	0.99
Receptor status						
ER positive	44,298	35,969	0.510	0.442	0.98 (0.80–1.21)	0.88
ER negative	44,298	9,343	0.510	0.503	1.21 (0.87–1.68)	0.26
Triple negative	44,298	4,017	0.510	0.448	1.26 (0.76–2.06)	0.37

Table 1. Association of *HOXB13* p.G84E with breast cancer risk in women of European descent. N, number; CAF, carrier allele frequency; OR, odds ratio; CI, confidence interval; BC, breast cancer; ER, estrogen receptor. *Dominant genetic model adjusted for country, age and principal components. Not all BCAC studies had info on all variables.

Furthermore, we wanted to replicate our findings for the p.G84E mutation. Therefore, we have genotyped 68,521 breast cancer cases and 54,865 controls from 81 studies in the Breast Cancer Association Consortium (BCAC) for the *HOXB13* p.G84E and p.R217C mutations.

Results

The CAF for the p.G84E mutation varies among different populations. In Asian and African BCAC studies, the p.G84E mutation was not detected, while the CAF was highest in Northern European countries (*i.e.* Sweden, Denmark and the Netherlands in controls) (Supplementary Table S1). Therefore, we restricted our analysis for the p.G84E mutation to 54,731 cases and 44,298 controls from European countries with a CAF that was larger than zero. In the overall analysis, the p.G84E mutation was not associated with breast cancer risk in Europeans (OR = 1.033, 95% CI = 0.857–1.244, $P = 0.734$; Table 1) in agreement with our previous study. We also performed analyses in which we enriched for high-risk subgroups such as women who were diagnosed before 50 years of age, premenopausal women and women with a family history of breast cancer or contralateral breast cancer. We also performed analyses by receptor status to evaluate whether *HOXB13* p.G84E associates with subtype-specific breast cancer risk. However, we did neither find any association between *HOXB13* p.G84E and the risk of breast cancer in any of these high-risk subgroups, nor did we find an association with subtype-specific breast cancer risk (Table 1).

Although in our previous study we found that the *HOXB13* p.R217C mutation was 3.5-fold more prevalent in cases than controls, the association between p.R217C and breast cancer risk was not statistically significant and the estimation of the risk was not very precise. Therefore, we evaluated the association of p.R217C with breast cancer risk in the 81 BCAC studies. Similar to p.G84E, the CAF for p.R217C varied among different populations. It was absent in both cases and controls of Asian ancestry, but not those of European and African ancestry. The CAF was highest in Macedonia, the Netherlands and Greece in controls (Supplementary Table S1). We analyzed 54,752 breast cancer patients and 44,422 controls from European countries with a CAF that was larger than zero. In the overall analysis, p.R217C was not associated with an increased breast cancer risk in European women (OR = 0.798, 95% CI = 0.482–1.322, $P = 0.381$; Table 2). Likewise, high-risk subgroup analyses and analyses by receptor status also did not reveal any association between *HOXB13* p.R217C and (subtype-specific) breast cancer risk (Table 2).

In our previous study we had sequenced the entire coding region of *HOXB13* in 1,250 familial non-*BRCA1/2* breast cancer patients and 800 controls and identified two other, less frequent, *HOXB13* missense mutations: p.P190L (*i.e.* NM_006361.6: c.569 C > T; NP_006352.2:p.(P190L)) and p.R268Q (*i.e.* NM_006361.6:c.803 G > A; NP_006352.2:p.(R268Q); rs748782183:C > T)²². These two mutations had not been investigated before due to their low frequency in the Dutch population. However, the present study enabled us to assess their frequency in a global context. The p.P190L mutation was most prevalent in the African population and absent in the Asian population (Supplementary Table S1). In the Europeans, we identified only four breast cancer patients and four controls carrying this mutation. The low population frequency in Europeans and the low sample size in Africans precluded any reliable analysis of an association with breast cancer risk. The p.R268Q mutation was absent in Asian and African BCAC studies. In Europeans, we identified only two breast cancer patients and two controls carrying this mutation, again precluding any reliable analysis of an association with breast cancer risk (Supplementary Table S1).

	N Controls	N Cases	CAF (%) Controls	CAF (%) Cases	OR (95% CI) *	P-value*
Overall analysis						
Europeans	44,422	54,752	0.077	0.062	0.80 (0.48–1.32)	0.38
Subgroup analysis						
Age of diagnosis						
< 50 years	44,422	17,669	0.077	0.045	0.38 (0.14–1.01)	0.05
Menopausal status						
Premenopausal	44,422	12,195	0.077	0.057	0.59 (0.24–1.44)	0.25
Family history						
1 st degree relative with BC	41,909	7,531	0.069	0.013	0.21 (0.03–1.53)	0.12
Second BC						
Contralateral BC	38,346	2,137	0.076	0.047	0.43 (0.05–3.43)	0.43
Receptor status						
ER positive	44,422	35,930	0.077	0.061	0.81 (0.46–1.42)	0.46
ER negative	44,422	9,343	0.077	0.064	0.82 (0.33–2.03)	0.66
Triple negative	44,422	4,045	0.077	0.025	0.29 (0.04–2.19)	0.23

Table 2. Association of *HOXB13* p.R217C with breast cancer risk in women of European descent. N, number; CAF, carrier allele frequency; OR, odds ratio; CI, confidence interval; BC, breast cancer; ER, estrogen receptor. *Dominant genetic model adjusted for country, age and principal components. Not all BCAC studies had info on all variables.

Discussion

We genotyped four *HOXB13* missense mutations: p.G84E, p.P190L, p.R217C and p.R268Q in 68,521 breast cancer cases and 54,865 controls from 81 studies in the BCAC on the OncoArray. All mutations were present in Europeans, but not in Asians. The p.P190L and p.R217C mutations were also present in the African ancestry BCAC studies, but not p.G84E and p.R268Q. Both p.P190L and p.R268Q were too rare to be evaluated for their association with an increased breast cancer risk. There were sufficient carriers of *HOXB13* p.G84E and p.R217C to allow association analysis in Europeans, however, both mutations did not associate with breast cancer risk. Our study, by contrast with prostate cancer, shows that *HOXB13* is not a material breast cancer susceptibility gene.

The current study is by far the largest study that has been performed evaluating the association with an increased breast cancer risk for germline *HOXB13* mutation carriers. Previously, Alanee *et al.* had found evidence that *HOXB13* p.G84E conferred an increased breast cancer risk in 877 familial non-*BRCA1/2* mutation carriers and 1650 controls (OR = 5.7, 95% CI = 1.0–40.7, $P = 0.02$)¹⁹. However, in a larger study conducted by Akbari *et al.*, no such association between the p.G84E mutation and an increased breast cancer risk was observed among 4,037 cases, of which 1,082 were familial, and 2,762 controls (OR = 1.2, 95% CI = 0.34–4.1, $P = 1.0$)²⁰. A study by Laitinen *et al.* consisting of 986 breast cancer patients (*i.e.* 323 familial non-*BRCA1/2* carriers and 663 unselected breast cancer patients) and 1,449 controls also did not reveal an association for overall breast cancer risk and p.G84E among Finnish women²¹. Results of these three studies have been pooled in a fixed-effects meta-analysis by Cai *et al.* and did not find a significant association between *HOXB13* p.G84E and an increased breast cancer risk (OR = 1.42, 95% CI = 0.78–2.61, $P = 0.26$)⁷. We also did not observe an increased breast cancer risk associated with the p.G84E mutation in our previous study of 3,270 familial non-*BRCA1/2* breast cancer cases and 2,327 controls (OR = 0.81, 95% CI = 0.41–1.59, $P = 0.54$)²². The results of the current study concur with these observations in that *HOXB13* p.G84E does not appear to act as a breast cancer susceptibility allele, neither in overall analyses (OR = 1.035, 95% CI = 0.859–1.246, $P = 0.718$) nor in analyses enriching for particular (high-risk) subgroups.

Besides p.G84E, we also identified p.R217C to be a recurrent mutation in the female Dutch population²². Since the estimation of the breast cancer risk for this mutation was not very precise in our previous study, we sought to re-evaluate the association between p.R217C and increased breast cancer risk in the current study. As for p.G84E, we did not find any association between p.R217C and an increased breast cancer risk, neither in overall analyses (OR = 0.798, 95% CI = 0.482–1.322, $P = 0.381$), nor in subgroup analyses. Interestingly, the p.R217C mutation had been described before among a few prostate cancer cases, but Xu *et al.* reported that p.R217C did not co-segregate with prostate cancer in the two families they identified^{23,24}. In concordance with this, OncoArray summary association results from the PRACTICAL consortium show that, indeed, p.R217C is also not a material prostate cancer susceptibility allele (OR = 1.32, 95% CI = 0.57–2.07), while p.G84E is associated with an increased prostate cancer risk in this data set (OR = 4.23, 95% CI = 4.03–4.42)²⁵.

Although *HOXB13* plays an important role in both breast and prostate cancer progression^{10,11,13–17}, germline mutations in the *HOXB13* gene seem to associate with the development of prostate cancer only^{5–8}. This suggests distinct biological pathways associated with *HOXB13* function in breast and prostate tissue. In prostate cancer, *HOXB13* co-localizes with AR and acts as a repressor of AR target genes to modulate AR hormonal responses^{26,27}. In breast cancer, ER and *HOXB13* have been shown to regulate each other's expression^{17,28}. Thus, in both tissue types hormonal responses are closely interlinked with *HOXB13* function. More research is needed, however, to understand better the differential roles of *HOXB13* in disease initiation and progression.

To conclude, in our large study consisting of 68,521 invasive breast cancer cases and 54,865 controls from 81 BCAC studies we provide strong evidence that the rare, but recurrent *HOXB13* germline mutations p.G84E and p.R217C are not associated with an increased risk to develop breast cancer. *HOXB13* is therefore not a material breast cancer susceptibility gene.

Materials and Methods

Study population. In this study, BCAC consists of 81 case-control studies of unrelated women with participants of European, Asian and African ancestry contributing 68,521 patients with invasive breast cancer and 54,865 controls^{2,3}. All studies provided core data on disease status and age at diagnosis while only a subset of the studies provided data on menopausal status, ER, PR and ERBB2 status, family history and bilateral breast cancer. All 81 BCAC studies were approved by their relevant governing research ethics committee and all participants provided written informed consent. The experimental protocol was approved by the Medical Ethical Committee of the Erasmus Medical Center Rotterdam and the study was carried out in accordance with the Code of Conduct of the Federation of Medical Scientific Societies in the Netherlands (<https://www.federa.org/gedragcodes>).

OncoArray genotyping. Genotyping of the 81 BCAC studies was performed previously using the OncoArray, a custom-designed Illumina Infinium BeadChip. About half of the approximately 533,000 OncoArray SNPs were selected as a 'GWAS backbone' (Illumina HumanCore) with the remainder of SNPs selected by the disease-based consortia representing the main cancer sites (e.g. breast, ovarian, prostate, lung, colorectal) for several distinct reasons as detailed in²⁹. Approximately 72,000 SNPs were selected specifically for their relevance to breast cancer. Details of the genotype calling and quality control for OncoArray are described elsewhere^{2,29}. In brief, samples were excluded when the call rate was below 95% or when these were probable duplicates, close relatives or samples with extreme heterozygosity. Ancestry was computed using a principal component analysis (PCA). Variants were excluded using the following criteria: an overall call rate <99% or <95% in any consortium, minor allele frequency (MAF) < 0.001, poor intensity and clustering metrics, deviation from the expected frequency as observed in the 1000 Genomes Project and deviation from the Hardy-Weinberg equilibrium (HWE; $P < 10^{-7}$ in controls or $P < 10^{-12}$ in cases). A total of 494,763 SNPs passed the quality control and included the following four *HOXB13* missense variants: c.251 G > A (p.G84E; rs138213197), c.569 C > T (p.P190L), c.649 C > T (p.R217C; rs139475791) and c.803 G > A (p.R268Q).

Statistical analyses. The association between *HOXB13* mutations and invasive breast cancer risk was evaluated using dominant genetic models by logistic regression analysis adjusting for country, age and principal components in European women. Subgroup analyses for the p.G84E and p.R217C variants were based on enriching for high-risk subgroups (i.e. women diagnosed with breast cancer <50 years, premenopausal women, women with a family history of breast cancer (i.e. 1st degree relative with breast cancer) and women diagnosed with a contralateral breast cancer) as well as stratification for hormone receptor status (i.e. ER positive, ER negative, triple negative) to evaluate subtype-specific breast cancer risk. All *P*-values were two-sided and $P < 0.05$ was considered to be statistically significant after correction for multiple testing by the Bonferroni procedure. Logistic regression analyses were performed using R version 3.3.3.

Data availability

OncoArray summary statistics from the BCAC are available at <http://bcac.ccge.medschl.cam.ac.uk/bcacdata/oncoarray/gwas-icogs-and-oncoarray-summary-results/>. Per-sample genotype data, core demographic data and data on diagnosis and pathology can be requested via the BCAC Data Access Co-ordinating Committee (DACC) at <http://bcac.ccge.medschl.cam.ac.uk/bcacdata/>. OncoArray summary statistics from the PRACTICAL consortium are available at http://practical.icr.ac.uk/blog/?page_id=8088.

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Additional information

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Correspondence and requests for materials should be addressed to A.H.

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NBCS Collaborators

Kristine K. Sahlberg^{53,55}, Anne-Lise Børresen-Dale^{53,54}, Lars Ottestad⁵³, Rolf Kåresen^{54,56}, Ellen Schlichting⁵⁶, Marit Muri Holmen⁵⁷, Toril Sauer⁵⁸, Vilde Haakensen⁵³, Olav Engebråten^{54,59}, Bjørn Naume⁶⁰, Alexander Fosså⁶⁰, Cecile E. Kiserud⁶¹, Kristin V. Reinertsen⁶¹, Åslaug Helland^{53,60}, Margit Riis⁵³, Jürgen Geisler⁶², OSBREAC* & Grethe I. Grenaker Alnæs⁵³

⁵³Department of Cancer Genetics, Institute for Cancer Research, Oslo University Hospital-Radiumhospitalet, Oslo, Norway. ⁵⁴Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway. ⁵⁵Department of Research, Vestre Viken Hospital, Drammen, Norway. ⁵⁶Section for Breast- and Endocrine Surgery, Department of Cancer, Division of Surgery, Cancer and Transplantation Medicine, Oslo University Hospital-Ullevål, Oslo, Norway. ⁵⁷Department of Radiology and Nuclear Medicine, Oslo University Hospital, Oslo, Norway. ⁵⁸Department of Pathology, Akershus University Hospital, Lørenskog, Norway. ⁵⁹Department of Tumor Biology, Institute for Cancer Research, Oslo University Hospital, Oslo, Norway. ⁶⁰Department of Oncology, Division of Surgery, Cancer and Transplantation Medicine, Oslo University Hospital-Radiumhospitalet, Oslo, Norway. ⁶¹National Advisory Unit on Late Effects after Cancer Treatment, Oslo University Hospital-Radiumhospitalet, Oslo, Norway. ⁶²Department of Oncology, Akershus University Hospital, Lørenskog, Norway.

OSBREAC

Tone F. Bathen¹⁷⁶, Elin Borgen¹⁷⁷, Britt Fritzman¹⁷⁸, Øystein Garred¹⁷⁷, Gry Aarum Geitvik⁵³, Solveig Hofvind^{179,180}, Anita Langerød⁵³, Ole Christian Lingjærde^{181,182}, Gunhild Mari Mælandsmo^{59,183}, Hege G Russnes^{53,177}, Helle Kristine Skjerven¹⁸⁴ & Therese Sørli⁵³

¹⁷⁶Department of Circulation and Medical Imaging, Norwegian University of Science and Technology (NTNU), Trondheim, Norway. ¹⁷⁷Department of Pathology, Oslo University Hospital, Oslo, Norway. ¹⁷⁸Østfold Hospital, Østfold, Norway. ¹⁷⁹Cancer Registry of Norway, Oslo, Norway. ¹⁸⁰Akershus University College of Applied Sciences, Faculty of Health Science, Oslo, Norway. ¹⁸¹Centre for Cancer Biomedicine, University of Oslo, Oslo, Norway. ¹⁸²Department of Computer Science, University of Oslo, Oslo, Norway. ¹⁸³Department of Pharmacy, Faculty of Health Sciences, University of Tromsø, Tromsø, Norway. ¹⁸⁴Breast and Endocrine Surgery, Department of Breast and Endocrine Surgery, Vestre Viken Hospital, Drammen, Norway.

ABCTB Investigators

Christine Clarke¹⁶³, Deborah Marsh¹⁶⁴, Rodney Scott^{165,166}, Robert Baxter¹⁶⁷, Desmond Yip^{168,169}, Jane Carpenter¹⁷⁰, Alison Davis^{171,172}, Nirmala Pathmanathan^{173,174}, Peter Simpson¹⁷⁵, Dinny Graham¹⁶³ & Mythily Sachchithanathan¹⁶³

¹⁶³Centre for Cancer Research, The Westmead Institute for Medical Research, The University of Sydney, Sydney, New South Wales, Australia. ¹⁶⁴Translational Oncology Group, School of Life Sciences, Faculty of Science, University of Technology Sydney, Sydney, New South Wales, Australia. ¹⁶⁵School of Biomedical Sciences, University of Newcastle, Newcastle, UK. ¹⁶⁶Hunter Medical Research Institute and NSW Health Pathology North, Newcastle, Australia. ¹⁶⁷Kolling Institute of Medical Research, University of Sydney, Sydney, New South Wales, Australia. ¹⁶⁸Epigenetics and Transcription Laboratory, Melanie Swan Memorial Translational Centre, Sci-Tech, University of Canberra, Canberra, Australian Capital Territory, Australia. ¹⁶⁹Department of Medical Oncology, The Canberra Hospital, Canberra, Australia. ¹⁷⁰Scientific Platforms, The Westmead Institute for Medical Research, University of Sydney, Sydney, New South Wales, Australia. ¹⁷¹The Canberra Hospital, Canberra, Australia. ¹⁷²The Australian National University, Canberra, Australia. ¹⁷³Westmead Breast Cancer Institute, Western Sydney Local Health District, Sydney, New South Wales, Australia. ¹⁷⁴University of Sydney, Western Clinical School, Sydney, New South Wales, Australia. ¹⁷⁵UQ Centre for Clinical Research, Faculty of Medicine, The University of Queensland, Brisbane, Australia.