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Two truncating variants in *FANCC* and breast cancer risk

Thilo Dörk¹, Paolo Peterlongo², Arto Mannermaa^{3,4,5}, Manjeet K. Bolla⁶, Qin Wang⁶, Joe Dennis⁶, Thomas Ahearn⁷, Irene L. Andrulis^{8,9}, Hoda Anton-Culver¹⁰, Volker Arndt¹¹, Kristan J. Aronson¹², Annelie Augustinsson¹³, Laura E. Beane Freeman⁷, Matthias W. Beckmann¹⁴, Alicia Beeghly-Fadiel¹⁵, Sabine Behrens¹⁶, Marina Bermisheva¹⁷, Carl Blomqvist^{18,19}, Natalia V. Bogdanova^{1,20,21}, Stig E. Bojesen^{22,23,24}, Hiltrud Brauch^{25,27,156}, Hermann Brenner^{11,27,28}, Barbara Burwinkel^{29,30}, Federico Canzian³¹, Tsun L. Chan^{32,33}, Jenny Chang-Claude^{16,34}, Stephen J. Chanock⁷, Ji-Yeob Choi^{35,36}, Hans Christiansen²⁰, Christine L. Clarke³⁷, Fergus J. Couch³⁸, Kamila Czene³⁹, Mary B. Daly⁴⁰, Isabel dos-Santos-Silva⁴¹, Miriam Dwek⁴², Diana M. Eccles⁴³, Arif B. Ekici⁴⁴, Mikael Eriksson³⁹, D. Gareth Evans^{45,46}, Peter A. Fasching^{14,47}, Jonine Figueroa^{7,48,49}, Henrik Flyger⁵⁰, Lin Fritschi⁵¹, Marike Gabrielson³⁹, Manuela Gago-Dominguez^{52,53}, Chi Gao^{54,55}, Susan M. Gapstur⁵⁶, Montserrat Garcia-Closas^{7,57}, José A. Garcia-Sáenz⁵⁸, Mia M. Gaudet⁵⁶, Graham G. Giles^{59,60,61}, Mark S. Goldberg^{62,63}, David E. Goldgar⁶⁴, Pascal Guénel⁶⁵, Lothar Haeberle⁶⁶, Christopher A. Haiman⁶⁷, Niclas Håkansson⁶⁸, Per Hall^{39,69}, Ute Hamann⁷⁰, Mikael Hartman^{71,72}, Jan Hauke^{73,74,75}, Alexander Hein¹⁴, Peter Hillemanns¹, Frans B. L. Hogervorst⁷⁶, Maartje J. Hooning⁷⁷, John L. Hopper⁶⁰, Tony Howell⁷⁸, Dezheng Huo⁷⁹, Hidemi Ito^{80,81}, Motoki Iwasaki⁸², Anna Jakubowska^{83,84}, Wolfgang Janni⁸⁵, Esther M. John⁸⁶, Audrey Jung¹⁶, Rudolf Kaaks¹⁶, Daehee Kang^{35,36,87}, Pooja Middha Kapoor^{16,88}, Elza Khusnutdinova^{17,89}, Sung-Won Kim⁹⁰, Cari M. Kitahara⁹¹, Stella Koutros⁷, Peter Kraft^{54,55}, Vessela N. Kristensen^{92,93}, Ava Kwong^{32,94,95}, Diether Lambrechts^{96,97}, Loic Le Marchand⁹⁸, Jingmei Li⁹⁹, Sara Lindström^{100,101}, Martha Linet⁹¹, Wing-Yee Lo^{25,26}, Jirong Long¹⁵, Artitaya Lophatananon¹⁰³, Jan Lubinski⁸³, Mehdi Manoochehri⁷⁰, Siranoush Manoukian¹⁰⁴, Sara Margolin^{69,105}, Elena Martinez^{53,106}, Keitaro Matsuo^{80,81}, Dimitris Mavroudis¹⁰⁷, Alfons Meindl¹⁰⁸, Usha Menon¹⁰⁹, Roger L. Milne^{59,60,110}, Nur Aishah Mohd Taib¹¹¹, Kenneth Muir^{102,103}, Anna Marie Mulligan^{112,113}, Susan L. Neuhausen¹¹⁴, Heli Nevanlinna¹¹⁵, Patrick Neven¹¹⁶, William G. Newman^{45,46}, Kenneth Offit^{117,118}, Olufunmilayo I. Olopade⁷⁹, Andrew F. Olshan¹¹⁹, Janet E. Olson¹²⁰, Håkan Olsson¹³, Sue K. Park^{35,36,87}, Tjoung-Won Park-Simon¹, Julian Peto⁴¹, Dijana Plaseska-Karanfilska¹²¹, Esther Pohl-Rescigno^{73,74,75}, Nadege Presneau⁴², Brigitte Rack⁸⁵, Paolo Radice¹²², Muhammad U. Rashid^{70,123}, Gad Rennert¹²⁴, Hedy S. Rennert¹²⁴, Atocha Romero¹²⁵, Matthias Ruebner⁶⁶, Emmanouil Saloustros¹²⁶, Marjanka K. Schmidt^{127,128}, Rita K. Schmutzler^{73,74,75}, Michael O. Schneider⁶⁶, Minouk J. Schoemaker¹²⁹, Christopher Scott¹²⁰, Chen-Yang Shen^{130,131}, Xiao-Ou Shu¹⁵, Jacques Simard¹³², Susan Slager¹²⁰, Snezhana Smichkoska¹³³, Melissa C. Southey^{110,134}, John J. Spinelli^{135,136}, Jennifer Stone^{60,137}, Harald Surowy^{29,30}, Anthony J. Swerdlow^{129,138}, Rulla M. Tamimi^{54,55,139}, William J. Tapper¹⁴⁰, Soo H. Teo^{111,141}, Mary Beth Terry¹⁴², Amanda E. Toland¹⁴³, Rob A. E. M. Tollenaar¹⁴⁴, Diana Torres^{70,145}, Gabriela Torres-Mejía¹⁴⁶, Melissa A. Troester¹¹⁹, Thérèse Truong⁶⁵, Shoichiro Tsugane¹⁴⁷, Michael Untch¹⁴⁸, Celine M. Vachon¹⁴⁹, Ans M. W. van den Ouweland¹⁵⁰, Elke M. van Veen^{45,46}, Joseph Vijai^{117,118}, Camilla Wendt¹⁰⁵, Alicja Wolk^{68,151}, Jyh-Cherng Yu¹⁵², Wei Zheng¹⁵, Argyrios Ziogas¹⁰, Elad Ziv¹⁵³, ABCTB Investigators*, NBCS Collaborators*, Alison M. Dunning¹⁶⁵, Paul D. P. Pharoah^{6,165}, Detlev Schindler¹⁶⁶, Peter Devilee^{167,168} & Douglas F. Easton^{6,165}

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¹Gynaecology Research Unit, Hannover Medical School, Hannover, Germany. ²Genome Diagnostics Program, IFOM - the FIRC Institute of Molecular Oncology, Milan, Italy. ³Translational Cancer Research Area, University of Eastern Finland, Kuopio, Finland. ⁴Institute of Clinical Medicine, Pathology and Forensic Medicine, University of Eastern Finland, Kuopio, Finland. ⁵Imaging Center, Department of Clinical Pathology, Kuopio University Hospital, Kuopio, Finland. ⁶Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK. ⁷Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, MD, USA. ⁸Fred A. Litwin Center for Cancer Genetics, Lunenfeld-Tanenbaum Research Institute of Mount Sinai Hospital, Toronto, ON, Canada. ⁹Department of Molecular Genetics, University of Toronto, Toronto, ON, Canada. ¹⁰Department of Epidemiology, Genetic Epidemiology Research Institute, University of California Irvine, Irvine, CA, USA. ¹¹Division of Clinical Epidemiology and Aging Research, C070, German Cancer Research Center (DKFZ), Heidelberg, Germany. ¹²Department of Public Health Sciences, and Cancer Research Institute, Queen's University, Kingston, ON, Canada. ¹³Department of Cancer Epidemiology, Clinical Sciences, Lund University, Lund, Sweden. ¹⁴Department of Gynecology and Obstetrics, Comprehensive Cancer Center ER-EMN, University Hospital Erlangen, Friedrich-Alexander-University Erlangen-Nuremberg, Erlangen, Germany. ¹⁵Division of Epidemiology, Department of Medicine, Vanderbilt Epidemiology Center, Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Nashville, TN, USA. ¹⁶Division of Cancer Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany. ¹⁷Institute of Biochemistry and Genetics of the Ufa Federal Research Centre of the Russian Academy of Sciences, Ufa, Russia. ¹⁸Department of Oncology, Helsinki University Hospital, University of Helsinki, Helsinki, Finland. ¹⁹Department of Oncology, Örebro University Hospital, Örebro, Sweden. ²⁰Department of Radiation Oncology, Hannover Medical School, Hannover, Germany. ²¹N.N. Alexandrov Research Institute of Oncology and Medical Radiology, Minsk, Belarus. ²²Copenhagen General Population Study, Herlev and Gentofte Hospital, Copenhagen University Hospital, Herlev, Denmark. ²³Department of Clinical Biochemistry, Herlev and Gentofte Hospital, Copenhagen University Hospital, Herlev, Denmark. ²⁴Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark. ²⁵Dr. Margarete Fischer-Bosch-Institute of Clinical Pharmacology, Stuttgart, Germany. ²⁶University of Tübingen, Tübingen, Germany. ²⁷German Cancer Consortium (DKTK), German Cancer Research Center (DKFZ), Heidelberg, Germany. ²⁸Division of Preventive Oncology, German Cancer Research Center (DKFZ) and National Center for Tumor Diseases (NCT), Heidelberg, Germany. ²⁹Molecular Epidemiology Group, C080, German Cancer Research Center (DKFZ), Heidelberg, Germany. ³⁰Molecular Biology of Breast Cancer, University Womens Clinic Heidelberg, University of Heidelberg, Heidelberg, Germany. ³¹Genomic Epidemiology Group, German Cancer Research Center (DKFZ), Heidelberg, Germany. ³²Hong Kong Hereditary Breast Cancer Family Registry, Cancer Genetics Centre, Happy Valley, Hong Kong. ³³Department of Pathology, Hong Kong Sanatorium and Hospital, Happy Valley, Hong Kong. ³⁴Cancer Epidemiology Group, University Cancer Center Hamburg (UCCH), University Medical Center Hamburg-Eppendorf, Hamburg, Germany. ³⁵Department of Biomedical Sciences, Seoul National University Graduate School, Seoul, Korea. ³⁶Cancer Research Institute, Seoul National University, Seoul, Korea. ³⁷Westmead Institute for Medical Research, University of Sydney, Sydney, New South Wales, Australia. ³⁸Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA. ³⁹Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden. ⁴⁰Department of Clinical Genetics, Fox Chase Cancer Center, Philadelphia, PA, USA. ⁴¹Department of Non-Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK. ⁴²Department of Biomedical Sciences, Faculty of Science and Technology, University of Westminster, London, UK. ⁴³Cancer Sciences Academic Unit, Faculty of Medicine, University of Southampton, Southampton, UK. ⁴⁴Institute of Human Genetics, University Hospital Erlangen, Friedrich-Alexander-University Erlangen-Nuremberg, Comprehensive Cancer Center Erlangen-EMN, Erlangen, Germany. ⁴⁵Division of Evolution and Genomic Sciences, School of Biological Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester Academic Health Science Centre, Manchester, UK. ⁴⁶Manchester Centre for Genomic Medicine, St Mary's Hospital, Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK. ⁴⁷David Geffen School of Medicine, Department of Medicine Division of Hematology and Oncology, University of California at Los Angeles, Los Angeles, CA, USA. ⁴⁸Usher Institute of Population Health Sciences and Informatics, The University of Edinburgh Medical School, Edinburgh, UK. ⁴⁹Cancer Research UK Edinburgh Centre, Edinburgh, UK. ⁵⁰Department of Breast Surgery, Herlev and Gentofte Hospital, Copenhagen University Hospital, Herlev, Denmark. ⁵¹School of Public Health, Curtin University, Perth, Western Australia, Australia. ⁵²Genomic 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. ⁵³Moore's Cancer Center, University of California San Diego, La Jolla, CA, USA. ⁵⁴Program in Genetic Epidemiology and Statistical Genetics, Harvard T.H. Chan School of Public Health, Boston, MA, USA. ⁵⁵Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA. ⁵⁶Behavioral and Epidemiology Research Group, American Cancer Society, Atlanta, GA, USA. ⁵⁷Division of Genetics and Epidemiology, Institute of Cancer Research, London, UK. ⁵⁸Medical Oncology Department, Hospital Clínico San Carlos, Instituto de Investigación Sanitaria San Carlos (IdISSC), Centro Investigación Biomédica en Red de Cáncer (CIBERONC), Madrid, Spain. ⁵⁹Cancer Epidemiology Division, Cancer Council Victoria, Melbourne, Victoria, Australia. ⁶⁰Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne, Melbourne, Victoria, Australia. ⁶¹Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Victoria, Australia. ⁶²Department of Medicine, McGill University, Montréal, QC, Canada. ⁶³Division of Clinical Epidemiology, Royal Victoria Hospital, McGill University, Montréal, QC, Canada. ⁶⁴Department of Dermatology, Huntsman Cancer Institute, University of Utah School of Medicine, Salt Lake City, UT, USA. ⁶⁵Cancer & Environment Group, Center for Research in Epidemiology and Population Health (CESP), INSERM, University Paris-Sud, University Paris-Saclay, Villejuif, France. ⁶⁶Department of Gynaecology and Obstetrics, University Hospital Erlangen, Friedrich-Alexander-University Erlangen-Nuremberg, Comprehensive Cancer Center Erlangen-EMN, Erlangen, Germany. ⁶⁷Department of Preventive Medicine, Keck School of Medicine, University of

Southern California, Los Angeles, CA, USA. ⁶⁸Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden. ⁶⁹Department of Oncology, Södersjukhuset, Stockholm, Sweden. ⁷⁰Molecular Genetics of Breast Cancer, German Cancer Research Center (DKFZ), Heidelberg, Germany. ⁷¹Saw Swee Hock School of Public Health, National University of Singapore, Singapore, Singapore. ⁷²Department of Surgery, National University Health System, Singapore, Singapore. ⁷³Center for Familial Breast and Ovarian Cancer, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany. ⁷⁴Center for Molecular Medicine Cologne (CMMC), Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany. ⁷⁵Center for Integrated Oncology (CIO), Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany. ⁷⁶Family Cancer Clinic, The Netherlands Cancer Institute - Antoni van Leeuwenhoek hospital, Amsterdam, The Netherlands. ⁷⁷Department of Medical Oncology, Family Cancer Clinic, Erasmus MC Cancer Institute, Rotterdam, The Netherlands. ⁷⁸Division of Cancer Sciences, University of Manchester, Manchester, UK. ⁷⁹Center for Clinical Cancer Genetics, The University of Chicago, Chicago, IL, USA. ⁸⁰Division of Cancer Epidemiology and Prevention, Aichi Cancer Center Research Institute, Nagoya, Japan. ⁸¹Division of Cancer Epidemiology, Nagoya University Graduate School of Medicine, Nagoya, Japan. ⁸²Division of Epidemiology, Center for Public Health Sciences, National Cancer Center, Tokyo, Japan. ⁸³Department of Genetics and Pathology, Pomeranian Medical University, Szczecin, Poland. ⁸⁴Independent Laboratory of Molecular Biology and Genetic Diagnostics, Pomeranian Medical University, Szczecin, Poland. ⁸⁵Department of Gynaecology and Obstetrics, University Hospital Ulm, Ulm, Germany. ⁸⁶Department of Medicine, Division of Oncology, Stanford Cancer Institute, Stanford University School of Medicine, Stanford, CA, USA. ⁸⁷Department of Preventive Medicine, Seoul National University College of Medicine, Seoul, Korea. ⁸⁸Faculty of Medicine, University of Heidelberg, Heidelberg, Germany. ⁸⁹Department of Genetics and Fundamental Medicine, Bashkir State University, Ufa, Russia. ⁹⁰Department of Surgery, Daerim Saint Mary's Hospital, Seoul, Korea. ⁹¹Radiation Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, USA. ⁹²Department of Cancer Genetics, Institute for Cancer Research, Oslo University Hospital-Radiumhospitalet, Oslo, Norway. ⁹³Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway. ⁹⁴Department of Surgery, The University of Hong Kong, Pok Fu Lam, Hong Kong. ⁹⁵Department of Surgery, Hong Kong Sanatorium and Hospital, Happy Valley, Hong Kong. ⁹⁶VIB Center for Cancer Biology, VIB, Leuven, Belgium. ⁹⁷Laboratory for Translational Genetics, Department of Human Genetics, University of Leuven, Leuven, Belgium. ⁹⁸Epidemiology Program, University of Hawaii Cancer Center, Honolulu, HI, USA. ⁹⁹Human Genetics Division, Genome Institute of Singapore, Singapore, Singapore. ¹⁰⁰Department of Epidemiology, University of Washington School of Public Health, Seattle, WA, USA. ¹⁰¹Public Health Sciences Division, Fred Hutchinson Cancer Research Center, Seattle, WA, USA. ¹⁰²Division of Health Sciences, Warwick Medical School, University of Warwick, Coventry, UK. ¹⁰³Division 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. ¹⁰⁴Unit of Medical Genetics, Department of Medical Oncology and Hematology, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milan, Italy. ¹⁰⁵Department of Clinical Science and Education, Södersjukhuset, Karolinska Institutet, Stockholm, Sweden. ¹⁰⁶Department of Family Medicine and Public Health, University of California San Diego, La Jolla, CA, USA. ¹⁰⁷Department of Medical Oncology, University Hospital of Heraklion, Heraklion, Greece. ¹⁰⁸Department of Gynecology and Obstetrics, Ludwig Maximilian University of Munich, Munich, Germany. ¹⁰⁹MRC Clinical Trials Unit at UCL, Institute of Clinical Trials & Methodology, University College London, London, UK. ¹¹⁰Precision Medicine, School of Clinical Sciences at Monash Health, Monash University, Clayton, Victoria, Australia. ¹¹¹Breast Cancer Research Unit, UM Cancer Research Institute, University of Malaya Medical Centre, Kuala Lumpur, Malaysia. ¹¹²Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, ON, Canada. ¹¹³Laboratory Medicine Program, University Health Network, Toronto, ON, Canada. ¹¹⁴Department of Population Sciences, Beckman Research Institute of City of Hope, Duarte, CA, USA. ¹¹⁵Department of Obstetrics and Gynecology, Helsinki University Hospital, University of Helsinki, Helsinki, Finland. ¹¹⁶Leuven Multidisciplinary Breast Center, Department of Oncology, Leuven Cancer Institute, University Hospitals Leuven, Leuven, Belgium. ¹¹⁷Clinical Genetics Research Lab, Department of Cancer Biology and Genetics, Memorial Sloan-Kettering Cancer Center, New York, NY, USA. ¹¹⁸Clinical Genetics Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY, USA. ¹¹⁹Department of Epidemiology, Gillings School of Global Public Health and UNC Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA. ¹²⁰Department of Health Sciences Research, Mayo Clinic, Rochester, MN, USA. ¹²¹Research Centre for Genetic Engineering and Biotechnology 'Georgi D. Efremov', Macedonian Academy of Sciences and Arts, Skopje, Republic of Macedonia. ¹²²Unit of Molecular Bases of Genetic Risk and Genetic Testing, Department of Research, Fondazione IRCCS Istituto Nazionale dei Tumori (INT), Milan, Italy. ¹²³Department of Basic Sciences, Shaukat Khanum Memorial Cancer Hospital and Research Centre (SKMCH & RC), Lahore, Pakistan. ¹²⁴Clalit National Cancer Control Center, Carmel Medical Center and Technion Faculty of Medicine, Haifa, Israel. ¹²⁵Medical Oncology Department, Hospital Universitario Puerta de Hierro, Madrid, Spain. ¹²⁶Department of Oncology, University Hospital of Larissa, Larissa, Greece. ¹²⁷Division of Molecular Pathology, The Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands. ¹²⁸Division of Psychosocial Research and Epidemiology, The Netherlands Cancer Institute - Antoni van Leeuwenhoek hospital, Amsterdam, The Netherlands. ¹²⁹Division of Genetics and Epidemiology, The Institute of Cancer Research, London, UK. ¹³⁰Institute of Biomedical Sciences, Academia Sinica, Taipei, Taiwan. ¹³¹School of Public Health, China Medical University, Taichung, Taiwan. ¹³²Genomics Center, Centre Hospitalier Universitaire de Québec – Université Laval Research Center, Québec City, QC, Canada. ¹³³Ss. Cyril and Methodius University in Skopje, Medical Faculty, University Clinic of Radiotherapy and Oncology, Skopje, Republic of Macedonia. ¹³⁴Department of Clinical Pathology, The University of Melbourne, Melbourne, Victoria, Australia. ¹³⁵Population Oncology, BC Cancer, Vancouver, BC, Canada. ¹³⁶School of Population and Public Health, University of British Columbia, Vancouver, BC, Canada. ¹³⁷The Curtin UWA Centre for Genetic Origins of Health and Disease, Curtin University and University of Western Australia, Perth, Western Australia, Australia. ¹³⁸Division of Breast Cancer Research, The Institute of Cancer Research, London, UK. ¹³⁹Channing Division of Network Medicine, Department of

Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA. ¹⁴⁰Faculty of Medicine, University of Southampton, Southampton, UK. ¹⁴¹Cancer Research Malaysia, Subang Jaya, Selangor, Malaysia. ¹⁴²Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY, USA. ¹⁴³Department of Cancer Biology and Genetics, The Ohio State University, Columbus, OH, USA. ¹⁴⁴Department of Surgery, Leiden University Medical Center, Leiden, The Netherlands. ¹⁴⁵Institute of Human Genetics, Pontificia Universidad Javeriana, Bogota, Colombia. ¹⁴⁶Center for Population Health Research, National Institute of Public Health, Mexico, Mexico. ¹⁴⁷Center for Public Health Sciences, National Cancer Center, Tokyo, Japan. ¹⁴⁸Department of Gynecology and Obstetrics, Helios Clinics Berlin-Buch, Berlin, Germany. ¹⁴⁹Department of Health Science Research, Division of Epidemiology, Mayo Clinic, Rochester, MN, USA. ¹⁵⁰Department of Clinical Genetics, Erasmus University Medical Center, Rotterdam, The Netherlands. ¹⁵¹Department of Surgical Sciences, Uppsala University, Uppsala, Sweden. ¹⁵²Department of Surgery, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan. ¹⁵³Department of Medicine, Institute for Human Genetics, UCSF Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA, USA. ¹⁵⁴Westmead Institute for Medical Research, University of Sydney, Sydney, New South Wales, Australia. ¹⁵⁵Department of Research, Vestre Viken Hospital, Drammen, Norway. ¹⁵⁶iFIT Cluster of Excellence, University of Tübingen, Tübingen, Germany. ¹⁵⁷Section for Breast- and Endocrine Surgery, Department of Cancer, Division of Surgery, Cancer and Transplantation Medicine, Oslo University Hospital-Ullevål, Oslo, Norway. ¹⁵⁸Department of Radiology and Nuclear Medicine, Oslo University Hospital, Oslo, Norway. ¹⁵⁹Department of Pathology, Akershus University Hospital, Lørenskog, Norway. ¹⁶⁰Department of Tumor Biology, Institute for Cancer Research, Oslo University Hospital, Oslo, Norway. ¹⁶¹Department of Oncology, Division of Surgery, Cancer and Transplantation Medicine, Oslo University Hospital-Radiumhospitalet, Oslo, Norway. ¹⁶²National Advisory Unit on Late Effects after Cancer Treatment, Oslo University Hospital-Radiumhospitalet, Oslo, Norway. ¹⁶³Department of Oncology, Akershus University Hospital, Lørenskog, Norway. ¹⁶⁴Breast Cancer Research Consortium, Oslo University Hospital, Oslo, Norway. ¹⁶⁵Centre for Cancer Genetic Epidemiology, Department of Oncology, University of Cambridge, Cambridge, UK. ¹⁶⁶Institute of Human Genetics, Biocenter, University of Würzburg, Würzburg, Germany. ¹⁶⁷Department of Pathology, Leiden University Medical Center, Leiden, The Netherlands. ¹⁶⁸Department of Human Genetics, Leiden University Medical Center, Leiden, The Netherlands. *A comprehensive list of consortium members appears at the end of the paper. Correspondence and requests for materials should be addressed to T.D. (email: doerk.thilo@mh-hannover.de)

Fanconi anemia (FA) is a genetically heterogeneous disorder with 22 disease-causing genes reported to date. In some FA genes, monoallelic mutations have been found to be associated with breast cancer risk, while the risk associations of others remain unknown. The gene for FA type C, *FANCC*, has been proposed as a breast cancer susceptibility gene based on epidemiological and sequencing studies. We used the Oncoarray project to genotype two truncating *FANCC* variants (p.R185X and p.R548X) in 64,760 breast cancer cases and 49,793 controls of European descent. *FANCC* mutations were observed in 25 cases (14 with p.R185X, 11 with p.R548X) and 26 controls (18 with p.R185X, 8 with p.R548X). There was no evidence of an association with the risk of breast cancer, neither overall (odds ratio 0.77, 95%CI 0.44–1.33, $p = 0.4$) nor by histology, hormone receptor status, age or family history. We conclude that the breast cancer risk association of these two *FANCC* variants, if any, is much smaller than for *BRCA1*, *BRCA2* or *PALB2* mutations. If this applies to all truncating variants in *FANCC* it would suggest there are differences between FA genes in their roles on breast cancer risk and demonstrates the merit of large consortia for clarifying risk associations of rare variants.

Fanconi Anemia (FA) is a rare recessively inherited disorder characterized by congenital malformations, progressive bone marrow failure and predisposition to cancer. Twenty-two different FA causative genes have now been identified whose products act in concert to mediate DNA interstrand crosslink repair^{1–3}. At least seven of them (*BRCA2/FANCD2*, *PALB2/FANCN*, *RAD51C/FANCO*, *RAD51/FANCR*, *BRCA1/FANCS*, *XRCC2/FANCU*, and *RFWD3/FANCW*) are involved in different stages of homology-directed recombinational DNA repair (HRR), a pathway for error-free maintenance of the genome during replication and after DNA damage. A number of FA genes (including *BRCA1/FANCS*, *BRCA2/FANCD1* and *PALB2/FANCN*) have been shown to be breast cancer susceptibility genes³. The products of *BRCA1*, *BRCA2*, and *PALB2* are central to early stages of HRR. Further interactors in this pathway, in particular *BRIP1/FANCI*, mainly have been linked to ovarian cancer risk^{4,5}. It is less known to what extent other FA gene products may play a role in the inherited component of breast cancer susceptibility. Few of these other FA genes have been tested for mutations in relatively small breast cancer case-control studies, thus far^{6–9}.

Early studies suggested that blood relatives of FA patients show an increased risk of breast cancer, although these findings have not been corroborated in a replication study and could not assess distinct FA complementation groups due to lack of genetic information at that time^{10–13}. After FA was stratified into subsets defined by complementation assays, an increased risk of breast cancer was attributed to heterozygous carriers of *FANCC* mutations¹³. Historically, this was the first of the FA genes to be identified and accounts for 8–15% of FA cases^{14–16}. More recently, *FANCC* has been suggested as a candidate breast cancer susceptibility gene in an exome sequencing study of 33 familial breast cancer cases and extension to another 438 cases¹⁷. However, the evidence for an association between *FANCC* and breast cancer risk is limited by the low prevalence of mutations^{17,18}, and much larger numbers of individuals are needed to provide sufficient power to detect associations of plausible magnitude¹⁹.

Mutation	Cases	Controls	Odds Ratio (95% CI)	p
p.R158X	14/64,778	18/49,810	0.64 (0.32; 1.29)	0.215
p.R548X	11/64,788	8/49,816	1.03 (0.41; 2.56)	0.942
All <i>FANCC</i>	25/64,760	26/49,793	0.77 (0.44; 1.33)	0.345

Table 1. Overall analysis of *FANCC* variants p.R158X and p.R548X. Association analyses of *FANCC* variants p.R158X and p.R548X with overall breast cancer risk. Results are given as odds ratios (OR) with 95% confidence interval (CI) and p-value (p).

In the present study, we genotyped two truncating variants of *FANCC* (p.R158X and p.R548X) using the Oncoarray (see Methods) in 64,760 female breast cancer cases and 49,793 female population controls of European descent. Both mutations are disease-causing in European FA patients and are recurrent in the FA mutation database²⁰.

Results

We identified the truncating *FANCC* variants p.R158X (rs121917783) and p.R548X (rs104886457) in 40 of 153,899 individuals and 20 of 153,904 individuals, respectively. All mutation carriers were heterozygotes. Carrier distributions per study and intensity cluster plots for Europeans (which included the majority of mutation carriers) are shown in Supplementary Table 1 and Supplementary Fig. 1, respectively. Since the majority of carriers were women of European ancestry, we restricted the subsequent case-control association analysis to participants from this population. Logistic regression analyses were adjusted for study and 15 principal components²¹.

In Europeans, the two *FANCC* variants were observed in 25/64,760 cases (14 with p.R158X, 11 with p.R548X) and in 26/49,793 controls (18 with p.R158X, 8 with p.R548X). There was no evidence of association between the *FANCC* variants and breast cancer risk, either for carriers of both variants combined (OR 0.77, 95%CI 0.44–1.33, $p = 0.35$), or for either variant individually (Table 1). Similarly, we found no evidence for an association with estrogen receptor (ER)-negative (OR 0.91, 0.35–2.37) or ER-positive (OR 0.67, 0.37–1.28) disease, nor for subsets of disease defined by age at diagnosis (<50 years), bilaterality, family history, histological morphology, grade or nodal status (Table 2).

For comparison, we also analysed the *PALB2/FANCN**p.R414X truncating variant that was genotyped in parallel on the same array. This variant was detected in 22/64,780 cases and 3/49,825 controls and was significantly associated with risk of breast cancer (OR 5.89, 95%CI 1.76–19.74, $p = 0.004$). The variant carriers were markedly enriched among cases with ER-negative tumours ($p = 9.4 \times 10^{-6}$; $p_{\text{diff}} = 0.0006$ in a log-likelihood ratio test) and specifically triple-negative breast tumours ($p = 3.8 \times 10^{-7}$; $p_{\text{diff}} = 0.0001$). The p.R414X truncating variant was also associated with ductal morphology, a positive first-degree family history of breast cancer, early age at diagnosis (<50 years), and low-differentiated tumours (grade 3) (Suppl. Table 1). Hence, by contrast with the two tested *FANCC* variants, p.R158X and p.R548X, the *FANCN/PALB2* variant p.R414X was strongly associated with overall and with ER-negative disease under the same genotyping and analysis conditions.

Discussion

Functional defects of DNA repair are a hallmark of genomic instability syndromes as well as of carcinogenesis. FA is a genome instability and cancer prone disorder that has been investigated for breast cancer predisposition in homozygotes and heterozygotes for more than three decades^{11,12}. Monoallelic mutations in five FA genes (*BRCA1*, *BRCA2*, *PALB2*, *RAD51C*, *BRIP1*) have now been confirmed to predispose to breast or ovarian cancer while biallelic mutations in these genes cause FA³. However, the role of the FA genes most commonly mutated, *FANCA* and *FANCC*, in the risk of developing breast cancer has remained uncertain. Epidemiological and segregation studies have provided some evidence of an increased breast cancer risk for grandmothers of FA patients, particularly those who carry the *FANCC* mutation¹³.

A previous sequencing study of Australian multiple-case breast cancer families had identified truncating variants in *FANCC* in 3 of 438 multiple-case breast cancer families but in none of 464 healthy controls, suggestive of a predisposing role for *FANCC* variants in breast cancer¹⁷. One of these variants, p.R158X, was also screened in our study. p.R158X was first reported shortly after the identification of the *FANCC* gene, and thus is one of the earliest recognized FA-causing mutations. Although representing an apparent nonsense mutation in exon 6, it also results in exon 6 being spliced out of a proportion of transcripts, suggesting this variant may alter splice site selection, with the aberrant transcript retaining the reading frame²². p.R548X, also an early-detected *FANCC* truncating variant²³, is an authentic stop mutation in exon 14, and although in the last exon, it proved to be clearly pathogenic for FA²⁴.

The fact that these two disease-causing variants have been frequently observed in European patients with FA²⁰ prompted us to investigate their association with breast cancer in a large case-control study. However, we did not observe a significant difference between their frequency among breast cancer cases and controls. The upper 95% confidence limit was 1.33, thus excluding a two-fold or greater increase in risk found for moderate- or high-penetrance alleles in predisposition genes such as *CHEK2* and *ATM*. Moreover, we found no evidence of association in subgroups defined by earlier age at onset, a positive family history of breast cancer, bilateral occurrence, or defined tumor parameters (histology, grade or hormone receptor status). However, confidence intervals for those estimates for subsets were wider as numbers were small – in particular we could not rule out a 2-fold increased risk for ER-negative or triple-negative breast cancer.

In contrast, we observed a clear association between the *PALB2/FANCN* variant p.R414X and breast cancer risk. *PALB2* is an established breast cancer susceptibility gene, and the investigated mutation p.R414X²⁵ occurred

Stratum	Cases	Odds Ratio (95% CI)	p
ER-negative	5/10,124	0.91 (0.35; 2.37)	0.845
ER-positive	14/40,855	0.67 (0.37; 1.28)	0.223
TNBC	2/4,126	0.89 (0.21; 3.77)	0.877
Ductal	6/36,695	0.33 (0.13; 0.80)	0.014
Lobular	4/6,842	1.27 (0.43; 3.69)	0.665
High grade	3/14,582	0.39 (0.12; 1.31)	0.129
Node-positive	1/15,937	0.14 (0.02; 1.00)	0.050
Familial	7/9,720	1.01 (0.43; 2.35)	0.988
Premenopausal	12/22,232	1.09 (0.55; 2.16)	0.814
Bilateral	0/2,741	—	0.645

Table 2. Analysis of *FANCC* variants (p.R158X and p.R548X combined) by tumour subtype. Association analyses of *FANCC* variants p.R158X and p.R548X with breast cancer risk for subgroups. Results are given as odds ratios (OR) with 95% confidence interval (CI) and p-value (p). Cases in subgroups were compared to the frequency 26/ 49,793 for all controls (derived from Table 1). Familial cases were defined as those with a first-degree family history of breast cancer; premenopausal cases were those with age at diagnosis <50 years. ER, estrogen-receptor; TNBC, triple-negative breast cancer.

at a similar frequency to the tested *FANCC* mutations. The observed six-fold enrichment of p.R414X in breast cancer patients is in line with previous findings for other *PALB2* founder mutations^{26–28} and in the upper range of the overall mutational effect size in *PALB2* case-control sequencing studies^{29,30}. We confirmed stronger associations with ER-negative breast cancer, with familial breast cancer and with a high tumor grade³¹. While genotyping arrays such as the Oncoarray are primarily used for evaluating common variants, these data confirm that the array provides a robust platform for evaluating even very rare alleles.

Although *PALB2* and *FANCC* are both FA genes, their products exert different roles in the recognition and repair of DNA damage. *FANCC* is a component of the FA core complex which is thought to recognize an inter-strand crosslink. *FANCL*, an E3 ubiquitin ligase in the core complex, ubiquitinates *FANCI* and *FANCD2*. After many nuclease and translesion polymerase steps, a DNA double stranded intermediate is formed and its repair requires proteins from the homology-directed repair pathway, including *FANCD1/BRCA2* and *FANCN/PALB2*. While truncating variants in *BRCA2* and *PALB2* confer a substantial risk of breast cancer, our study suggests that truncating *FANCC* variants do not confer a comparable risk. It is possible that members of the FA core complex that act upstream of HRR are less relevant for breast cancer due to their more specialized function in the repair of crosslinks while *BRCA1*, *BRCA2*, and *PALB2* function more globally at DNA double-strand breaks. On the other hand, there is some evidence that truncating mutations in another gene involved in the early detection of intra-strand crosslinks, *FANCM*, are associated with both breast and ovarian cancer risk^{32–34}, though *FANCM* is part of an anchor complex rather than the FA core complex and is not considered a classical FA gene^{35,36}. It is also possible that the two prototype *FANCC* truncating variants analysed here, despite being FA-causing, have reduced penetrance for breast cancer due to some residual function, and other particular *FANCC* variants may confer a more substantial risk. More work will be required to clarify the role of each FA core complex member for breast cancer susceptibility.

In conclusion, our study findings suggest important differences between FA genes, indicating that truncating variants in *FANCC* do not confer a high overall risk of breast cancer unlike *PALB2*, *BRCA1* and *BRCA2*. Our study does not exclude a role of monoallelic *FANCC* variants as low-penetrance alleles for breast cancer or as a genetic risk factor for certain breast cancer subgroups. Very large datasets, such as those generated through the BCAC, are critical to evaluate such rare mutations.

Methods

Patients. A total of 87 studies from the Breast Cancer Association Consortium (BCAC), of which 78 were case-control studies (some nested within prospective cohort studies) and 9 were case-only studies, contributed data as summarized in Supplementary Table 1. All studies provided data on disease status and age at diagnosis/observation, and the majority provided information on clinico-pathological and epidemiological factors, which have been curated and incorporated into the BCAC database (version 6). All participating studies were approved by their appropriate ethics review boards and all subjects provided informed consent. A list of the ethics review boards by study is provided in Supplementary Table 3.

Genotyping. The Illumina OncoArray design and genotyping procedure have been described previously^{21,37}. In brief, approximately 72,000 variants were selected, among others, for inclusion on the array specifically for their potential relevance to breast cancer, based on prior evidence of association with overall or subtype-specific disease, with breast density or with breast tissue specific gene expression. After genotype calling and quality control of the cluster file, variants with a call rate <95% in any consortium, not in Hardy-Weinberg equilibrium ($P < 10^{-7}$ in controls or $P < 10^{-12}$ in cases) or with concordance <98% among 5,280 duplicate pairs were excluded. We also excluded samples with extreme heterozygosity (>4.89 standard deviations [SD] from the mean for the respective ethnicity). The final dataset, before restriction based on ethnicity, consisted of 153,673 samples of which 89,733 were cases and 63,940 were controls.

Statistical analyses. Per-allele odds ratios and 95% confidence intervals were generated using logistic regression with adjustment for principal components and study. Principal component analysis was performed using data for 33,661 uncorrelated SNPs (which included 2,318 markers of continental ancestry) with a MAF \geq 0.05 and maximum correlation of 0.1, using purpose-written PCCalc software (written by Jonathan Tyrer and available at <http://ccge.medschl.cam.ac.uk/software/pccalc/>).

We also estimated subtype-specific per-allele ORs after restricting the cases by hormone receptor and/or HER2/neu status, by tumor grade, by ductal or lobular morphology, by nodal status, by bilateral occurrence of the tumor, by early diagnosis ($<$ 50 years), and by first-degree family history of breast cancer, using available BCAC data for the cases. Since we analysed 3 variants across 10 subgroups, a two-sided p-value \leq 0.016 for the overall analyses and a two-sided p-value \leq 0.0016 for the subgroup analyses were considered nominally significant.

Ethical approval. All experimental protocols were approved by the respective ethical institutions of participating BCAC centers. The study was carried out in accordance with the Declaration of Helsinki, and informed consent was obtained from all study participants.

Data Availability

The genotyping results from the Oncoarray are available in the dbGAP repository. The *FANCC* variants analysed in the current study are deposited in the NCBI SNP database as rs121917783 and rs104886457. The datasets analysed during the current study are available from the corresponding author upon reasonable request and with permission of the Data Access Committee of the Breast Cancer Association Consortium.

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Author Contributions

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Consortia ABCTB Investigators

Rosemary Balleine¹⁶⁹, Robert Baxter¹⁷⁰, Stephen Braye¹⁷¹, Jane Carpenter¹⁵⁴, Jane Dahlstrom^{172,173}, John Forbes¹⁷⁴, C. Soon Lee¹⁷⁵, Deborah Marsh¹⁷⁶, Adrienne Morey¹⁷⁷, Nirmala Pathmanathan¹⁷⁸, Rodney Scott^{179,180}, Peter Simpson¹⁸¹, Allan Spigelman¹⁸², Nicholas Wilcken^{183,184}, Desmond Yip^{173,185} & Nikolajs Zeps¹⁸⁶

NBCS Collaborators

Anne-Lise Børresen-Dale^{92,93}, Grethe I. Grenaker Alnæs⁹², Kristine K. Sahlberg^{92,155,164}, Lars Ottestad⁹², Rolf Kåresen^{93,157}, Ellen Schlichting¹⁵⁷, Marit Muri Holmen¹⁵⁸, Toril Sauer^{93,159}, Vilde Haakensen⁹², Olav Engebråten^{93,160,161}, Bjørn Naume^{93,161}, Alexander Fosså^{161,162}, Cecile E. Kiserud^{161,162}, Kristin V. Reinertsen^{161,162}, Åslaug Helland^{92,161}, Margit Riis¹⁵⁷ & Jürgen Geisler^{93,163}

¹⁶⁹Pathology West ICPMR, Westmead, Sydney, NSW, Australia. ¹⁷⁰Kolling Institute of Medical Research, University of Sydney, Royal North Shore Hospital, Sydney, NSW, Australia. ¹⁷¹Pathology North, John Hunter Hospital, Newcastle, NSW, Australia. ¹⁷²Department of Anatomical Pathology, ACT Pathology, Canberra Hospital, Canberra, ACT, Australia. ¹⁷³ANU Medical School, Australian National University, Canberra, ACT, Australia. ¹⁷⁴Department of Surgical Oncology, Calvary Mater Newcastle Hospital, Australian New Zealand Breast Cancer Trials Group, and School of Medicine and Public Health, University of Newcastle, Newcastle, NSW, Australia. ¹⁷⁵School of Science and Health, The University of Western Sydney, Sydney, NSW, Australia. ¹⁷⁶Hormones and Cancer Group, Kolling Institute of Medical Research, Royal North Shore Hospital, University of Sydney, Sydney, NSW, Australia. ¹⁷⁷SydPath St Vincent's Hospital, Sydney, NSW, Australia. ¹⁷⁸Department of Tissue Pathology and Diagnostic Oncology, Pathology West, Westmead Breast Cancer Institute, Westmead Hospital, Sydney, NSW, Australia. ¹⁷⁹Centre for Information Based Medicine, Hunter Medical Research Institute, Newcastle, NSW, Australia. ¹⁸⁰Priority Research Centre for Cancer, School of Biomedical Sciences and Pharmacy, Faculty of Health, University of Newcastle, Newcastle, NSW, Australia. ¹⁸¹The University of Queensland: UQ Centre for Clinical Research and School of Medicine, Brisbane, QLD, Australia. ¹⁸²Hereditary Cancer Clinic, St Vincent's Hospital, The Kinghorn Cancer Centre, Sydney, NSW, Australia. ¹⁸³Crown Princess Mary Cancer Centre, Westmead Hospital, Sydney, NSW, Australia. ¹⁸⁴Sydney Medical School - Westmead, University of Sydney, Sydney, NSW, Australia. ¹⁸⁵Department of Medical Oncology, The Canberra Hospital, Canberra, ACT, Australia. ¹⁸⁶St John of God Perth Northern Hospitals, Perth, WA, Australia.