Received: 30 October 2017 | Revised: 9 January 2018 | Accepted: 19 January 2018

DOI: 10.1002/humu.23406

SPECIAL ARTICLE

WILEY HGVS HUMAN GENOME VARIATION SOCIETY

Mutational spectrum in a worldwide study of 29,700 families with *BRCA1* or *BRCA2* mutations

Timothy R. Rebbeck[1] | Tara M. Friebel[1] | Eitan Friedman[2] | Ute Hamann[3] | Dezheng Huo[4] | Ava Kwong[5] | Edith Olah[6] | Olufunmilayo I. Olopade[4] | Angela R. Solano[7] | Soo-Hwang Teo[8] | Mads Thomassen[9] | Jeffrey N. Weitzel[10] | TL Chan[11] | Fergus J. Couch[12] | David E. Goldgar[13] | Torben A. Kruse[9] | Edenir Inêz Palmero[14] | Sue Kyung Park[15,16,17] | Diana Torres[3,18] | Elizabeth J. van Rensburg[19] | Lesley McGuffog[20] | Michael T. Parsons[21] | Goska Leslie[20] | Cora M. Aalfs[22] | Julio Abugattas[23] | Julian Adlard[24] | Simona Agata[25] | Kristiina Aittomäki[26] | Lesley Andrews[27] | Irene L. Andrulis[28,29] | Adalgeir Arason[36] | Norbert Arnold[30] | Banu K. Arun[31] | Ella Asseryanis[32] | Leo Auerbach[32] | Jacopo Azzollini[33] | Judith Balmaña[34] | Monica Barile[35] | Rosa B. Barkardottir[36] | Daniel Barrowdale[20] | Javier Benitez[37,38] | Andreas Berger[39] | Raanan Berger[40] | Amie M. Blanco[41] | Kathleen R. Blazer[10] | Marinus J. Blok[42] | Valérie Bonadona[43] | Bernardo Bonanni[35] | Angela R. Bradbury[44] | Carole Brewer[45] | Bruno Buecher[46] | Saundra S. Buys[47] | Trinidad Caldes[48] | Almuth Caliebe[49] | Maria A. Caligo[50] | Ian Campbell[51] | Sandrine M. Caputo[46] | Jocelyne Chiquette[52] | Wendy K. Chung[53] | Kathleen B.M. Claes[54] | J. Margriet Collée[55] | Jackie Cook[56] | Rosemarie Davidson[57] | Miguel de la Hoya[48] | Kim De Leeneer[54] | Antoine de Pauw[46] | Capucine Delnatte[58] | Orland Diez[59] | Yuan Chun Ding[60] | Nina Ditsch[61] | Susan M. Domchek[44] | Cecilia M. Dorfling[19] | Carolina Velazquez[62] | Bernd Dworniczak[63] | Jacqueline Eason[64] | Douglas F. Easton[20] | Ros Eeles[65] | Hans Ehrencrona[66] | Bent Ejlertsen[67] | EMBRACE[20] | Christoph Engel[68] | Stefanie Engert[69] | D. Gareth Evans[70] | Laurence Faivre[71] | Lidia Feliubadaló[72] | Sandra Fert Ferrer[73] | Lenka Foretova[74] | Jeffrey Fowler[75] | Debra Frost[20] | Henrique C. R. Galvão[76] | Patricia A. Ganz[77] | Judy Garber[78] | Marion Gauthier-Villars[46] | Andrea Gehrig[79] | GEMO Study Collaborators[80,81] | Anne-Marie Gerdes[82] | Paul Gesta[83] | Giuseppe Giannini[84] | Sophie Giraud[85] | Gord Glendon[86] | Andrew K. Godwin[87] | Mark H. Greene[88] | Jacek Gronwald[89] | Angelica Gutierrez-Barrera[31] | Eric Hahnen[90] | Jan Hauke[90] | HEBON[91] | Alex Henderson[92] | Julia Hentschel[93] | Frans B.L. Hogervorst[94] | Ellen Honisch[95] | Evgeny N. Imyanitov[96] | Claudine Isaacs[97] |

 © 2018 Wiley Periodicals, Inc.

Louise Izatt[98] | Angel Izquierdo[99] | Anna Jakubowska[89] | Paul James[100] | Ramunas Janavicius[101] | Uffe Birk Jensen[102] | Esther M. John[103,104] | Joseph Vijai[105] | Katarzyna Kaczmarek[89] | Beth Y. Karlan[106] | Karin Kast[107] | KConFab Investigators[108] | Sung-Won Kim[109] | Irene Konstantopoulou[110] | Jacob Korach[111] | Yael Laitman[2] | Adriana Lasa[112] | Christine Lasset[43] | Conxi Lázaro[72] | Annette Lee[113] | Min Hyuk Lee[114] | Jenny Lester[106] | Fabienne Lesueur[115] | Annelie Liljegren[116] | Noralane M. Lindor[117] | Michel Longy[118] | Jennifer T. Loud[119] | Karen H. Lu[120] | Jan Lubinski[89] | Eva Machackova[74] | Siranoush Manoukian[33] | Véronique Mari[121] | Cristina Martínez-Bouzas[122] | Zoltan Matrai[123] | Noura Mebirouk[115] | Hanne E.J. Meijers-Heijboer[124] | Alfons Meindl[69] | Arjen R. Mensenkamp[125] | Ugnius Mickys[126] | Austin Miller[127] | Marco Montagna[25] | Kirsten B. Moysich[128] | Anna Marie Mulligan[129] | Jacob Musinsky[105] | Susan L. Neuhausen[60] | Heli Nevanlinna[130] | Joanne Ngeow[131] | Huu Phuc Nguyen[132] | Dieter Niederacher[95] | Henriette Roed Nielsen[9] | Finn Cilius Nielsen[133] | Robert L. Nussbaum[134] | Kenneth Offit[135] | Anna Öfverholm[136] | Kai-ren Ong[137] | Ana Osorio[138] | Laura Papi[139] | Janos Papp[6] | Barbara Pasini[140] | Inge Sokilde Pedersen[141] | Ana Peixoto[142,143] | Nina Peruga[89] | Paolo Peterlongo[144] | Esther Pohl[90] | Nisha Pradhan[105] | Karolina Prajzendanc[89] | Fabienne Prieur[145] | Pascal Pujol[146] | Paolo Radice[147] | Susan J. Ramus[148,149] | Johanna Rantala[150] | Muhammad Usman Rashid[3,151] | Kerstin Rhiem[90] | Mark Robson[152] | Gustavo C. Rodriguez[153] | Mark T. Rogers[154] | Vilius Rudaitis[155] | Ane Y. Schmidt[133] | Rita Katharina Schmutzler[90] | Leigha Senter[156] | Payal D. Shah[44] | Priyanka Sharma[157] | Lucy E. Side[158] | Jacques Simard[159] | Christian F. Singer[32] | Anne-Bine Skytte[102] | Thomas P. Slavin[10] | Katie Snape[160] | Hagay Sobol[161] | Melissa Southey[161,162] | Linda Steele[60] | Doris Steinemann[163] | Grzegorz Sukiennicki[89] | Christian Sutter[164] | Csilla I. Szabo[165] | Yen Y. Tan[39] | Manuel R. Teixeira[142,143] | Mary Beth Terry[166] | Alex Teulé[167] | Abigail Thomas[168] | Darcy L. Thull[169] | Marc Tischkowitz[170] | Silvia Tognazzo[25] | Amanda Ewart Toland[171] | Sabine Topka[105] | Alison H Trainer[172] | Nadine Tung[173] | Christi J. van Asperen[174] | Annemieke H. van der Hout[175] | Lizet E. van der Kolk[176] | Rob B. van der Luijt[177] | Mattias Van Heetvelde[54] | Liliana Varesco[178] | Raymonda Varon-Mateeva[179] | Ana Vega[180] | Cynthia Villarreal-Garza[181,182] | Anna von Wachenfeldt[183] | Lisa Walker[184] | Shan Wang-Gohrke[185] | Barbara Wappenschmidt[90] | Bernhard H. F. Weber[186] | Drakoulis Yannoukakos[110] | Sook-Yee Yoon[8] | Cristina Zanzottera[33] | Jamal Zidan[187] | Kristin K. Zorn[188] |

Christina G. Hutten Selkirk[189] | Peter J. Hulick[190] | Georgia Chenevix-Trench[21] | Amanda B. Spurdle[21] | Antonis C. Antoniou[20] | Katherine L. Nathanson[44]

[1]Harvard TH Chan School of Public Health and Dana Farber Cancer Institute, Boston, USA

[2]The Susanne Levy Gertner Oncogenetics Unit, Institute of Human Genetics, Chaim Sheba Medical Center, Ramat Gan 52621, and the Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel

[3]Molecular Genetics of Breast Cancer, German Cancer Research Center (DKFZ), Heidelberg, Germany

[4]Center for Clinical Cancer Genetics and Global Health, University of Chicago, Chicago, USA

[5]The Hong Kong Hereditary Breast Cancer Family Registry, Cancer Genetics Center, Hong Kong Sanatorium and Hospital, Hong Kong, China

[6]Department of Molecular Genetics, National Institute of Oncology, Budapest, Hungary

[7]INBIOMED, Faculty of Medicine, University of Buenos Aires/CONICET and CEMIC, Department of Clinical Chemistry, Medical Direction, Buenos Aires, Argentina

[8]Cancer Research Initiatives Foundation, Sime Darby Medical Centre, Subang Jaya, Malaysia

[9]Department of Clinical Genetics, Odense University Hospital, Odense, Denmark

[10]Division of Clinical Cancer Genomics, City of Hope Cancer Center, California, USA

[11]Division of Molecular Pathology, Department of Pathology, Hong Kong Sanatorium & Hospital, Happy Valley, Hong Kong

[12]Department of Laboratory Medicine and Pathology, and Health Sciences Research, Rochester, USA

[13]Department of Dermatology, University of Utah School of Medicine, Salt Lake City, USA

[14]Molecular Oncology Research Center, Barretos Cancer Hospital, São Paulo, Brazil

[15]Department of Preventive Medicine, Seoul National University College of Medicine, Seoul, Korea

[16]Department of Biomedical Science, Seoul National University Graduate School, Seoul, Korea

[17]Cancer Research Center, Seoul National University, Seoul, Korea

[18]Institute of Human Genetics, Pontificia Universidad Javeriana, Colombia

[19]Cancer Genetics Laboratory, Department of Genetics, University of Pretoria, South Africa

[20]Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK

[21]Genetics and Computational Biology Department, QIMR Berghofer Medical Research Institute, Brisbane, Australia

[22]Department of Clinical Genetics, Academic Medical Center, Amsterdam, The Netherlands

[23]City of Hope Clinical Cancer Genomics Community Research Network, Duarte, USA

[24]Yorkshire Regional Genetics Service, Chapel Allerton Hospital, Leeds, UK

[25]Immunology and Molecular Oncology Unit, Veneto Institute of Oncology IOV - IRCCS, Padua, Italy

[26]Department of Clinical Genetics, Helsinki University Hospital, Helsinki, Finland

[27]Hereditary Cancer Clinic, Prince of Wales Hospital, Randwick, Australia

[28]Lunenfeld-Tanenbaum Research Institute, Toronto, Canada

[29]Department of Molecular Genetics, University of Toronto, Toronto, Canada

[30]Department of Gynaecology & Oncology, Medical University of Vienna, Austria

[31]Department of Breast Medical Oncology and Clinical Cancer Genetics Program, University Of Texas MD Anderson Cancer Center, Houston, USA

[32]Dept of OB/GYN and Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria

[33]Unit of Medical Genetics, Department of Medical Oncology and Hematology, Fondazione IRCCS (Istituto Di Ricovero e Cura a Carattere Scientifico) Instituto Nazionale Tumori (INT), Milan, Italy

[34]Department of Medical Oncology, Vall d'Hebron University Hospital, Barcelona, Spain

[35]Division of Cancer Prevention and Genetics, Istituto Europeo di Oncologia (IEO), Milan, Italy

[36]Laboratory of Cell Biology, Department of Pathology, hus 9, Landspitali-LSH v/Hringbraut, 101 Reykjavik, Iceland and BMC (Biomedical Centre), Faculty of Medicine, University of Iceland, Reykjavik, Iceland

[37]Human Genetics Group and Genotyping Unit (CEGEN), Human Cancer Genetics Programme, Spanish National Cancer Research Centre (CNIO), Madrid, Spain

[38]Biomedical Network on Rare Diseases (CIBERER), Madrid, Spain

[39]Dept of OB/GYN, Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria

[40]The Institute of Oncology, Chaim Sheba Medical Center, Ramat Gan, Israel

[41]UCSF Cancer Genetics and Prevention Program, San Francisco, USA

[42]Department of Clinical Genetics, Maastricht University Medical Center, Maastricht, The Netherlands

[43]Unité de Prévention et d'Epidémiologie Génétique, Centre Léon Bérard, 28 rue Laënnec, Lyon, France

[44]Department of Medicine, Abramson Cancer Center, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, USA

[45]Department of Clinical Genetics, Royal Devon & Exeter Hospital, Exeter, UK

[46]Service de Génétique, Institut Curie, 26 rue d'Ulm, Paris, France

[47]Department of Medicine, Huntsman Cancer Institute, Salt Lake City, USA

[48]Molecular Oncology Laboratory, Hospital Clinico San Carlos, Instituto de Investigación Sanitaria San Carlos (IdISSC), Centro Investigación Biomédica en Red de Cáncer (CIBERONC), Madrid, Spain

[49]Institute of Human Genetics, University Hospital of Schleswig-Holstein, Kiel, Germany

[50]Section of Molecular Genetics, Dept. of Laboratory Medicine, University Hospital of Pisa, Pisa, Italy

[51]Research Division, Peter MacCallum Cancer Centre, Melbourne, Australia

[52]CRCHU de Quebec-oncologie, Centre des maladies du sein Deschênes-Fabia, Hôpital du Saint-Sacrement, Sainte-Foy, Canada

[53]Departments of Pediatrics and Medicine, Columbia University, New York, USA

[54]Center for Medical Genetics, Ghent University, Gent, Belgium

[55]Department of Clinical Genetics, Family Cancer Clinic, Erasmus University Medical Center, Rotterdam, The Netherlands

[56]Sheffield Clinical Genetics Service, Sheffield Children's Hospital, Sheffield, UK

[57]Department of Clinical Genetics, South Glasgow University Hospitals, Glasgow, UK

[58]Unité d'oncogénétique, ICO-Centre René Gauducheau, Saint Herblain, France

[59]Oncogenetics Group, Vall d'Hebron Institute of Oncology (VHIO), Clinical and Molecular Genetics Area, Vall d'Hebron University Hospital, Barcelona, Spain

[60]Department of Population Sciences, Beckman Research Institute of City of Hope, Duarte, USA

[61]Department of Gynaecology and Obstetrics, Ludwig-Maximilian University, Munich, Germany

[62]Cáncer Hereditario, Instituto de Biología y Genética Molecular, IBGM, Universidad de Valladolid, Valladolid, Spain

[63]Institute of Human Genetics, University of Münster, Münster, Germany

[64]Nottingham Clinical Genetics Service, Nottingham University Hospitals NHS Trust, Nottingham, UK

[65]Oncogenetics Team, The Institute of Cancer Research and Royal Marsden NHS Foundation Trust, London, UK

[66]Department of Clinical Genetics, Lund University Hospital, Lund, Sweden

[67]Department of Oncology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark

[68]Institute for Medical Informatics, Statistics and Epidemiology, University of Leipzig, Leipzig, Germany

[69]Department of Gynaecology and Obstetrics, Division of Tumor Genetics, Klinikum rechts der Isar, Technical University, Munich, Germany

[70]Genomic Medicine, Manchester Academic Health Sciences Centre, Division of Evolution and Genomic Sciences, University of Manchester, Central Manchester University Hospitals NHS Foundation Trust, Manchester, UK

[71]Centre de Lutte Contre le Cancer Georges François Leclerc, France and Genomic and Immunotherapy Medical Institute, Dijon University Hospital, Dijon, France

[72]Molecular Diagnostic Unit, Hereditary Cancer Program, ICO-IDIBELL (Catalan Institute of Oncology-Bellvitge Biomedical Research Institute), Barcelona, Spain

[73]Laboratoire de Génétique Chromosomique, Hôtel Dieu Centre Hospitalier, Chambéry, France

[74]Department of Cancer Epidemiology and Genetics, Masaryk Memorial Cancer Institute, Brno, Czech Republic

[75]Columbus Cancer Council, Ohio State University, Columbus, USA

[76]Oncogenetics Department, Barretos Cancer Hospital, Barretos, Brazil

[77]UCLA Schools of Medicine and Public Health, Division of Cancer Prevention & Control Research, Jonsson Comprehensive Cancer Center, Los Angeles, USA

[78]Cancer Risk and Prevention Clinic, Dana-Farber Cancer Institute, Boston, USA

[79]Centre of Familial Breast and Ovarian Cancer, Department of Medical Genetics, Institute of Human Genetics, University of Würzburg, Germany, Würzburg

[80]Department of Tumour Biology, Institut Curie, Paris, France

[81]Institut Curie, Paris, France

[82]Department of Clinical Genetics, Copenhagen, Denmark

[83]Service Régional Oncogénétique Poitou-Charentes, Centre Hospitalier, Niort, France

[84]Department of Molecular Medicine, University La Sapienza, and Istituto Pasteur - Fondazione Cenci-Bolognetti, Rome, Italy

[85]Bâtiment Cheney D, Centre Léon Bérard, Lyon, France

[86]Ontario Cancer Genetics Network: Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, Toronto, Canada

[87]Department of Pathology and Laboratory Medicine, University of Kansas Medical Center, Kansas City, USA

[88]Clinical Genetics Branch, DCEG, NCI, NIH, Bethesda, USA

[89]Department of Genetics and Pathology, Pomeranian Medical University, Szczecin, Poland

[90]Center for Familial Breast and Ovarian Cancer, Center for Integrated Oncology (CIO), Medical Faculty, University Hospital Cologne, Cologne, Germany

[91]The Hereditary Breast and Ovarian Cancer Research Group Netherlands (HEBON), Netherlands Cancer Institute, Amsterdam, The Netherlands

[92]Institute of Genetic Medicine, Centre for Life, Newcastle Upon Tyne Hospitals NHS Trust, Newcastle upon Tyne, UK

[93]Institute of Human Genetics, University Leipzig, Leipzig, Germany

[94]Family Cancer Clinic, Netherlands Cancer Institute, Amsterdam, The Netherlands

[95]Department of Gynaecology and Obstetrics, University Hospital Düsseldorf, Heinrich-Heine University, Düsseldorf, Germany

[96]N.N. Petrov Institute of Oncology, St. Petersburg, Russia

[97]Lombardi Comprehensive Cancer Center, Georgetown University, Washington, USA

[98]Clinical Genetics, Guy's and St. Thomas' NHS Foundation Trust, London, UK

[99]Genetic Counseling Unit, Hereditary Cancer Program, IDIBGI (Institut d'Investigació Biomèdica de Girona), Catalan Institute of Oncology, Girona, Spain

[100]Parkville Familial Cancer Centre, Peter MacCallum Cancer Centre, Melbourne, Australia

[101]Hematology, oncology and transfusion medicine center, Dept. of Molecular and Regenerative Medicine, Vilnius University Hospital Santariskiu Clinics, Vilnius, Lithuania

[102]Department of Clinical Genetics, Aarhus University Hospital, Aarhus N, Denmark

[103]Department of Epidemiology, Cancer Prevention Institute of California, Fremont, USA

[104]Department of Health Research and Policy (Epidemiology) and Stanford Cancer Institute, Stanford University School of Medicine, Stanford, USA

[105]Clinical Genetics Research Laboratory, Dept. of Medicine, Memorial Sloan-Kettering Cancer Center, New York, USA

[106]Women's Cancer Program at the Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, USA

[107]Department of Gynecology and Obstetrics, Medical Faculty and University Hospital Carl Gustav Carus, Dresden, Germany

[108]Research Department, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia and The Sir Peter MacCallum Department of Oncology University of Melbourne, Parkville, Australia

[109]Department of Surgery, Daerim St. Mary's Hospital, Seoul, Korea

[110]Molecular Diagnostics Laboratory, INRASTES (Institute of Nuclear and Radiological Sciences and Technology), National Centre for Scientific Research "Demokritos", Athens, Greece

[111]The Gyneco-Oncology Department, Chaim Sheba Medical Center, Ramat Gan, Israel

[112]Servicio de Genética-CIBERER U705, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

[113]The Feinstein Institute for Medical Research, Manhasset, USA

[114]Department of Surgery, Soonchunhyang University and Seoul Hospital, Seoul, Korea

[115]Inserm U900, Institut Curie, PSL Research University, Paris, France

[116]Department of Oncology Radiumhemmet and Institution of Oncology and Patology, Karolinska University Hospital and Karolinska Institutet, Solna, Sweden

[117]Department of Health Sciences Research, Mayo Clinic, Scottsdale, USA

[118]Oncogénétique, Institut Bergonié, Bordeaux, France

[119]Clinical Genetics Branch, DCEG, NCI, NIH, Bethesda, USA

[120]Department of Gynecological Oncology and Clinical Cancer Genetics Program, University Of Texas MD Anderson Cancer Center, Houston, USA

[121]Centre Antoine Lacassagne, Nice, France

[122]Laboratorio de Genética Molecular, Servicio de Genética, Hospital Universitario Cruces, BioCruces Health Research Institute, Barakaldo, Spain

[123]Department of Surgery, National Institute of Oncology, Budapest, Hungary

[124]Department of Clinical Genetics, VU University Medical Center, Amsterdam, The Netherlands

[125]Department of Human Genetics, Radboud University Medical Center, Nijmegen, The Netherlands

[126]Vilnius university Santariskiu hospitalNational Center of Pathology, Vilnius, Lithuania

[127]NRG Oncology, Statistics and Data Management Center, Roswell Park Cancer Institute, Buffalo, USA

[128]Department of Cancer Prevention and Control, Roswell Park Cancer Institute, Buffalo, USA

[129]Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Canada

[130]Department of Obstetrics and Gynecology, University of Helsinki and Helsinki University Hospital, HUS, Finland

[131]Cancer Genetics Service, Division of Medical Oncology, National Cancer Centre Singapore, Bukit Merah, Singapore

[132]Institute of Medical Genetics and Applied Genomics, University of Tuebingen, Tuebingen, Germany

[133]Center for Genomic Medicine, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

[134]Cancer Genetics and Prevention Program, University of California San Francisco, San Francisco, USA

[135]Clinical Genetics Research Laboratory, Dept. of Medicine, Cancer Biology and Genetics, Memorial Sloan-Kettering Cancer Center, New York, USA

[136]Department of Clinical Genetics, Sahlgrenska University Hospital, Gothenburg, Sweden

[137]West Midlands Regional Genetics Service, Birmingham Women's Hospital Healthcare NHS Trust, Edgbaston, UK

[138]Human Genetics Group, Human Cancer Genetics Programme, Spanish National Cancer Research Centre (CNIO), Biomedical Network on Rare Diseases (CIBERER), Madrid, Spain

[139]Unit of Medical Genetics, Department of Biomedical, Experimental and Clinical Sciences, University of Florence, Florence, Italy

[140]Department of Medical Sciences, University of Turin, Turin, Italy

[141]Section of Molecular Diagnostics, Department of Biochemistry, Aalborg University Hospital, Aalborg, Denmark

[142]Department of Genetics, Portuguese Oncology Institute of Porto (IPO Porto), Porto, Portugal

[143]Biomedical Sciences Institute (ICBAS), University of Porto, Porto, Portugal

[144]IFOM, The FIRC (Italian Foundation for Cancer Research) Institute of Molecular Oncology, Milan, Italy

[145]Service de Génétique Clinique Chromosomique et Moléculaire, Hôpital Nord, St Etienne, France

[146]Unité d'Oncogénétique, CHU Arnaud de Villeneuve, Montpellier, France

[147]Unit of Molecular Bases of Genetic Risk and Genetic Testing, Department of Research, Fondazione IRCCS (Istituto Di Ricovero e Cura a Carattere Scientifico), Istituto Nazionale Tumori (INT), Milan, Italy

[148]School of Women's and Children's Health, UNSW, Sydney, Australia

[149]The Kinghorn Cancer Centre, Garvan Institute of Medical Research, Sydney, Australia

[150]Department of Clinical Genetics, Karolinska University Hospital, Stockholm, Sweden

[151]Department of Basic Sciences, Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan

[152]Clinical Genetics Services, Dept. of Medicine, Memorial Sloan-Kettering Cancer Center, New York, USA

[153]Division of Gynecologic Oncology, North Shore University Health System, University of Chicago, Evanston, USA

[154]All Wales Medical Genetics Services, University Hospital of Wales, Cardiff, UK

[155]Department of Gynecology, Vilnius University Hospital Santariskiu Clinics, Centre of Woman's Health and pathology, Vilnius, Lithuania

[156]Clinical Cancer Genetics Program, Division of Human Genetics, Department of Internal Medicine, The Comprehensive Cancer Center, The Ohio State University, Columbus, USA

[157]Department of Internal Medicine, Division of Oncology, University of Kansas Medical Center, Westwood, USA

[158]North East Thames Regional Genetics Service, Great Ormond Street Hospital for Children NHS Trust, London, UK

[159]Genomics Center, Centre Hospitalier Universitaire de Québec Research Center and Laval University, Quebec City, Canada

[160]Medical Genetics Unit, University of London, St George's, UK

[161]Département Oncologie Génétique, Prévention et Dépistage, Institut Paoli-Calmettes, Marseille Medical School-AM University, Marseille, France

[162]Genetic Epidemiology Laboratory, Department of Pathology, University of Melbourne, Parkville, Australia

[163]Institute of Cell and Molecular Pathology, Hannover Medical School, Hannover, Germany

[164]Institute of Human Genetics, University Hospital Heidelberg, Heidelberg, Germany

[165]National Human Genome Research Institute, National Institutes of Health, Bethesda, USA

[166]Department of Epidemiology, Columbia University, New York, USA

[167]Genetic Counseling Unit, Hereditary Cancer Program, IDIBELL (Bellvitge Biomedical Research Institute), Catalan Institute of Oncology, CIBERONC, Gran Via de l'Hospitalet, Barcelona, Spain

[168]Department of Health Sciences Research, Mayo Clinic, Rochester, USA

[169]Department of Medicine, Magee-Womens Hospital, University of Pittsburgh School of Medicine, Pittsburgh, USA

[170]Program in Cancer Genetics, Departments of Human Genetics and Oncology, McGill University, Montreal, Canada

[171]Division of Human Genetics, Departments of Internal Medicine and Cancer Biology and Genetics, Comprehensive Cancer Center, The Ohio State University, Columbus, USA

[172]Parkville Familial Cancer Centre, Royal Melbourne Hospital, Melbourne, Australia

[173]Department of Medical Oncology, Beth Israel Deaconess Medical Center, Massachusetts, USA

[174]Department of Clinical Genetics, Leiden University Medical Center, Leiden, The Netherlands

[175]Department of Genetics, University Medical Center, Groningen University, Groningen, The Netherlands

[176]Family Cancer Clinic, Netherlands Cancer Institute, Amsterdam, The Netherlands

[177]Department of Medical Genetics, University Medical Center, Utrecht, The Netherlands

[178]Unit of Hereditary Cancer, Department of Epidemiology, Prevention and Special Functions, IRCCS (Istituto Di Ricovero e Cura a Carattere Scientifico) AOU San Martino - IST Istituto Nazionale per la Ricerca sul Cancro, Genoa, Italy

[179]Institute of Human Genetics, Campus Virchov Klinikum, Berlin, Germany

[180]Fundación Pública Galega de Medicina Xenómica-SERGAS, Grupo de Medicina Xenómica-USC, CIBERER, IDIS, Santiago de Compostela, Spain

[181]Departamento de Investigacion y de Tumores Mamarios del, Instituto Nacional de Cancerologia, Mexico City, Mexico

[182]Centro de Cancer de Mama del Hospital Zambrano HellionTecnologico de Monterrey, San Pedro Garza Garcia, Mexico

[183]Department of Oncology, Karolinska University Hospital, Stockholm, Sweden

[184]Oxford Regional Genetics Service, Churchill Hospital, Oxford, UK

[185]Department of Gynaecology and Obstetrics, University Hospital, Ulm, Germany

[186]Institute of Human Genetics, Regensburg University, Regensburg, Germany

[187]Institute of Oncology, Rivka Ziv Medical Center, Zefat, Israel

[188]Magee-Womens Hospital, University of Pittsburgh School of Medicine, Pittsburgh, USA

[189]Center for Medical Genetics, North Shore University Health System, Evanston, USA

[190]Medical Director, Center for Medical Genetics, NorthShore University HealthSystem, Clinical Assistant Professor of Medicine, University of Chicago Pritzker School of Medicine, Evanston, USA

Correspondence
Timothy R. Rebbeck, PhD, 1101 Dana, 450 Brookline Avenue, Dana Farber Cancer Institute, Boston, MA 02215, USA.
Email: Timothy_Rebbeck@dfci.harvard.edu

Funding information
National Institutes of Health, Grant/Award Number: R01-CA102776

United States NIH, including NCI, funding supported the research presented in this manuscript.

Communicated by Stephen J. Chanock

Abstract

The prevalence and spectrum of germline mutations in *BRCA1* and *BRCA2* have been reported in single populations, with the majority of reports focused on White in Europe and North America. The Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA) has assembled data on 18,435 families with *BRCA1* mutations and 11,351 families with *BRCA2* mutations ascertained from 69 centers in 49 countries on six continents. This study comprehensively describes the characteristics of the 1,650 unique *BRCA1* and 1,731 unique *BRCA2* deleterious (disease-associated) mutations identified in the CIMBA database. We observed substantial variation in mutation type and frequency by geographical region and race/ethnicity. In addition to known founder mutations, mutations of relatively high frequency were identified in specific racial/ethnic or geographic groups that may reflect founder mutations and which could be used in targeted (panel) first pass genotyping for specific populations. Knowledge of the population-specific mutational spectrum in *BRCA1* and *BRCA2* could inform efficient strategies for genetic testing and may justify a more broad-based oncogenetic testing in some populations.

KEYWORDS
BRCA1, BRCA2, breast cancer, ethnicity, geography, mutation, ovarian cancer

1 | INTRODUCTION

Women who carry germline mutations in either *BRCA1* [MIM# 113705] or *BRCA2* [MIM# 600185] are at an increased risk of breast and ovarian cancers. Estimates of cancer risk associated with *BRCA1* and *BRCA2* mutations vary depending on the population studied. For mutations in *BRCA1*, the estimated average risk of breast and ovarian cancers ranges from 57 to 65% and 20 to 50%, respectively (Chen & Parmigiani, 2007; Kuchenbaecker et al., 2017). For *BRCA2*, average risk estimates range from 35 to 57% and 5 to 23%, respectively (Chen & Parmigiani, 2007; Kuchenbaecker et al., 2017). Mutation-specific cancer risks have been reported that suggest breast cancer cluster regions (BCCR) and ovarian cancer cluster regions (OCCR) exist in both *BRCA1* and *BRCA2* (Gayther et al., 1997; Kuchenbaecker et al., 2017; Rebbeck et al., 2015). The identification of mutations in *BRCA1* or *BRCA2* has important clinical implications, as knowledge of their presence is important for risk assessment and informs medical management for patients. Interventions, such as risk-reducing bilateral mastectomy and salpingo-oophorectomy or annual breast magnetic resonance imaging (MRI) screening, are available to women who carry deleterious *BRCA1* or *BRCA2* mutations to enable early detection of breast cancer and for active risk reduction by risk-reducing surgery (Domchek et al., 2010; Rebbeck et al., 2002; Saslow et al., 2007). The presence of *BRCA1* or *BRCA2* mutations can also influence cancer treatment decisions, principally around the use of platinum agents or poly(ADP-ribose) polymerase (PARP) inhibitors (Lord & Ashworth, 2017) or contralateral risk-reducing mastectomy. Increased numbers of women are having clinical genetic testing for *BRCA1* and *BRCA2* mutations, and recommendations continue to expand to whom testing should be offered (NCCN, 2017).

In Whites drawn from the general populations in North America and the United Kingdom, the prevalence of *BRCA1* and *BRCA2* mutations has been estimated around a broad range from 0.1 to 0.3% and 0.1 to 0.7%, respectively (Peto et al., 1999; Struewing et al., 1997; Whittemore et al., 2004). The Australian Lifepool study, studying a control population consisting of cancer-free women ascertained via population-based mammographic screening program, estimated the overall frequency of *BRCA1* and *BRCA2* mutations to be 0.65% (1:153), with *BRCA1* mutations at 0.20% (1:500) and *BRCA2* mutations at 0.45% (1:222) (Thompson et al., 2016). Estimates from the Exome Aggregation Consortium (ExAC) are similar, with frequencies of *BRCA1* and *BRCA2* mutations (excluding The Cancer Genome Atlas [TCGA] data) at 0.21% (1:480) and 0.31% (1:327), respectively; or combined at 0.51% (1:195) (Maxwell, Domchek, Nathanson, & Robson, 2016). As they do not include large genomic rearrangements, some newer population-based estimates may still underrepresent the total number of *BRCA1* and *BRCA2* mutations. Although the overall prevalence of *BRCA1* and *BRCA2* mutations in most general populations is low, many hundreds of thousands of yet-to-be-tested individuals worldwide carry these mutations.

The prevalence of founder mutations in some racial/ethnic groups is much higher. For example, the mutations *BRCA1* c.5266dup (5382insC), *BRCA1* c.68_69del (185delAG) and *BRCA2* c.5946del (6174delT) have a combined prevalence of 2–3% in U.S. Ashkenazi Jews (Roa, Boyd, Volcik, & Richards, 1996; Struewing et al., 1997; Whittemore et al., 2004). For these mutations, double heterozygotes in *BRCA1* and *BRCA2* also have been reported (Friedman et al., 1998; Moslehi et al., 2000; Ramus et al., 1997a; Rebbeck et al., 2016). Several other founder mutations have been identified, including the Icelandic founder mutation *BRCA2* c.771_775del (999del5) (Thorlacius et al., 1996), the French Canadian mutations *BRCA1* c.4327C > T (C4446T), the *BRCA2* c.8537_8538del (8765delAG) (Oros et al., 2006b; Tonin et al., 2001; Tonin, Mes-Masson, Narod, Ghadirian, & Provencher, 1999), the *BRCA1* mutations c.181T > G, and c.4034del in Central-Eastern Europe (Gorski et al., 2000), the *BRCA1* c.548-?–4185+?del in Mexico (Villarreal-Garza et al., 2015b; Weitzel et al., 2013),

the BRCA2 mutation c.9097dup in Hungary (Ramus et al., 1997b; Van Der Looij, et al., 2000), and others. These mutations represent the majority of mutations observed in these populations and have been confirmed as true founder mutations as they have common ancestral haplotypes (Neuhausen et al., 1996, 1998; Oros et al., 2006a). Recurrent mutations have been identified in other populations, but they represent a smaller proportion of all unique *BRCA1* and *BRCA2* mutations, and have not been characterized as true founder mutations. There are multiple recurrent mutations in Scandinavian, Dutch, French, and Italian populations (Ferla et al., 2007). Similarly, a number of recurrent mutations specific to non-European populations also have been reported in Hispanic/Mexican, African American, Middle Eastern, and Asian populations (Bu et al., 2016; Ferla et al., 2007; Kurian, 2010; Lang et al., 2017; Ossa & Torres, 2016; Villarreal-Garza et al., 2015b).

The mutational spectra in *BRCA1* and *BRCA2* are best delineated in Whites from Europe and North America. However, data on mutational spectra in non-White populations of Asian, African, Mediterranean, South American and Mexican Hispanic descent have also been reported (Abugattas et al., 2015; Ahn et al., 2007; Alemar et al., 2016; Bu et al., 2016; Eachkoti et al., 2007; Ferla et al., 2007; Gao et al., 2000; Gonzalez-Hormazabal et al., 2011; Ho et al., 2000; Jara et al., 2006; John et al., 2007; Kurian, 2010; Laitman et al., 2011; Lang et al., 2017; Lee et al., 2003; Li, et al., 2006; Nanda et al., 2005; Ossa & Torres, 2016; Pal, Permuth-Wey, Holtje, & Sutphen, 2004; Rodríguez et al., 2012; Seong et al., 2009; Sharifah et al., 2010; Solano et al., 2017; Song et al., 2005; Song et al., 2006; Toh et al., 2008; Torres et al., 2007; Troudi et al., 2007; Villarreal-Garza et al., 2015b; Vogel et al., 2007; Weitzel et al., 2005; Weitzel et al., 2007; Zhang et al., 2009). In the current study, we provide a global description of *BRCA1* and *BRCA2* mutations by geography and race/ethnicity from the investigators of the Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA).

2 | METHODS

Details of centers participating in CIMBA and data collection protocols have been reported previously (Antoniou et al., 2007). Details of the CIMBA initiative and information about the participating centers can be found at http://cimba.ccge.medschl.cam.ac.uk/ (Chenevix-Trench et al., 2007). All included mutation carriers participated in clinical or research studies at the host institutions after providing informed consent under IRB-approved protocols. Sixty-nine centers and multicenter consortia submitted data that met the CIMBA inclusion criteria (Antoniou et al., 2007). Only female carriers with pathogenic *BRCA1* and/or *BRCA2* mutations were included in the current analysis. One mutation carrier per family in the CIMBA database was included in this report. The actual family relationships (e.g., pedigrees) were not available, but a variable that defined family membership supplied by each center was used for this purpose. Less than 1% of families (86 of 29,700) had two family members with two different mutations. In these situations, each mutation observed in the family was included in the analysis. In the case of the 94 dual mutation carriers (i.e., individuals with both *BRCA1* and *BRCA2* mutations), one of the two mutations was chosen at random for inclusion in the analysis.

The CIMBA data set was used to describe the distribution of mutations by effect and function. For the remaining analyses, mutations were excluded if self-reported race/ethnicity data were missing. Pathogenicity of mutation was defined as follows: (1) generating a premature termination codon (PTC), except variants generating a PTC after codon 1854 in *BRCA1* and after codon 3309 of *BRCA2*, (2) large in-frame deletions that span one or more exons, and (3) deletion of transcription regulatory regions (promoter and/or first exon) expected to cause lack of expression of mutant allele. We also included missense variants considered pathogenic by using multifactorial likelihood approaches (Bernstein et al., 2006; Goldgar et al., 2004). Mutations that did not meet the above criteria but have been classified as pathogenic by Myriad Genetics, Inc. (Salt Lake City, UT) also were included. Classification of nonsense-mediated decay (NMD) was based on in-silico predictions and was not based on molecular classification (Anczukow et al., 2008).

Contingency table analysis using a chi-square test was used to test for differences in dichotomous variables, as was a *t*-test for continuous variables. Mutation counts are presented as the number of families with the mutation. Fisher's exact tests were used if sample sizes in any contingency table cell were less than five. Analyses were done in STATA, v. 14.2.

3 | RESULTS

3.1 | Mutations in *BRCA1* and *BRCA2*

From the 26,861 *BRCA1* and 16,954 *BRCA2* mutation carriers in the CIMBA data set as of June 2017, 18,435 families with *BRCA1* mutations and 11,351 families with *BRCA2* mutations were studied to count only one occurrence of a mutation per family. Figure 1 shows the countries that contributed mutations to this report. From among these families, 1,650 unique *BRCA1* and 1,731 unique *BRCA2* mutations were identified. The unique mutations and number of families in which each mutation was observed are listed in Supporting Information Table S1. In each gene, the five most common mutations (including founder mutations) accounted for 33% of all mutations in *BRCA1* (8,739 of 26,861 mutation carriers) and 19% of all mutations in *BRCA2* (3,244 of 16,954 mutation carriers). A website containing information about the most common mutations reported here can be found at: http://cimba.ccge.medschl.cam.ac.uk/. This information may be periodically updated as new data become available.

3.2 | Mutation type and effect

Table 1 presents a summary of the type of *BRCA1* or *BRCA2* mutations and their predicted effect on transcription and translation. The most common mutation type was frameshift followed by nonsense. The most common effect of *BRCA1* and *BRCA2* mutations was premature translation termination and most of the mutant mRNAs were predicted



FIGURE 1 Countries (in red) that provided data on BRCA1 and/or BRCA2 mutation carriers in this report. Race/ethnic breakdown is reported for countries with more than 100 observations with multiple ethnicities totaling at least 10% of the country's sample (i.e., Australia, Brazil, Canada, USA)

to undergo nonsense-mediated mRNA decay (Anczukow et al., 2008). Despite having the same spectrum of mutations in *BRCA1* and *BRCA2*, the frequency distribution by mutation type, effect, or function differed significantly ($p < .05$) between *BRCA1* and *BRCA2* mutation carriers for many groups, as shown in Table 1. These observed differences are largely because genomic rearrangements and missense mutations account for a much higher proportion of mutations in *BRCA1* when compared with *BRCA2*, as previously described (Welcsh & King, 2001).

We and others have found that BCCR and OCCR exist that may confer differential cancer risks (Gayther et al., 1997; Gayther et al., 1995; Kuchenbaecker et al., 2017; Rebbeck et al., 2015). Figure 2 reports the relative frequency of mutations in the BCCR and OCCR by race/ethnicity. Compared with Whites, we observed differences in the relative frequency of mutations in the *BRCA1* BCCR and OCCR in Asians and Hispanics, and in the *BRCA2* OCCR in Hispanics. To the degree that the mutations within the BCCRs and OCCRs conferred differential cancer risks, these data suggest that *BRCA1* and *BRCA2* mutation-associated cancer risks may vary by race/ethnicity.

3.3 | Geography and race/ethnicity

The most common mutations by country are summarized in Table 2 (*BRCA1*) and Table 3 (*BRCA2*). The locations of the mutations that were observed in African American, Asian, and Hispanic populations are depicted in Figure 3 (*BRCA1*) and Figure 4 (*BRCA2*). Some countries (Albania, Bosnia, Costa Rica, Ireland, Honduras, Japan, Norway, Peru, Philippines, Qatar, Saudi Arabia, Romania, Venezuela and Turkey) contributed fewer than 10 mutation carriers to the CIMBA database. Many of these mutations were submitted to the central database by CIMBA centers that ascertained these patients, but these patients originated from a different country. Based on such small numbers, it was impossible to make inferences about the relative importance of mutations in these locations. A description of the major ethnicity by country is provided in Supporting Information Table S2.

The mutational distribution among the major racial/ethnic groups and by geography is summarized in Tables 4 and 5. Table 4 includes only those individuals for whom self-identified race/ethnicity was recorded. Note that in some countries it is prohibited to collect data on race and ethnicity, so this information is missing. Among the 10 most common *BRCA1* mutations in each racial/ethnic group, a few were seen in several populations, including the recurrent Jewish and Eastern European founder mutations c.5266dup (5382insC) and c.68_69del (185delAG), c.815_824dup in African Americans and Hispanics, c.3756_3759del in White and Jewish individuals, and c.5503C > T and c.3770_3771del in Asians and Jews. Similarly, recurrent mutations in *BRCA2* included c.5946del (6174delT) in Whites and Jews, c.2808_2811del in Whites, African Americans, Asians, Hispanics, and Jews, c.6275_6276del in Whites and Hispanics, c.3847_3848del in Whites and Jews, c.658_659del in African Americans and Hispanics, and c.3264dup in Hispanics and Jews. The majority of other recurrent *BRCA1* and *BRCA2* mutations were only observed within a single racial/ethnic group, particularly African Americans, Asians, and Hispanics. Of note, the vast majority of women who self-identified as Jewish carry the Ashkenazi Jewish founder mutations *BRCA1* c.5266dup and c.68_69del and *BRCA2* c.5946del. Only 72 (3.9%) of 1,852 *BRCA1* mutation carrier families and 55 (5.6%) of 990 *BRCA2* mutation carrier families who self-identified as being Jewish carried other (nonfounder) mutations. However, since many individuals of self-identified Jewish ancestry are

TABLE 1 Characteristics of *BRCA1* and *BRCA2* mutations in the CIMBA database (by unique mutation)

			BRCA1 (*N* = 1,650)		*BRCA2* (*N* = 1,731)		
	Designation	**Definition**	***N***	**%**	**N**	**%**	***p*-value**
Mutation Type	Large Deletion (DL)	Genomic DNA deletion (encompassing at least 1 exon)	130	7.9	34	1.9	<.0001
	Large Duplication (DP)	Genomic DNA duplication (encompassing at least 1 exon)	27	1.6	11	0.6	.010
	Frameshift (FS)	Deletion or insertion resulting in a disruption of the open reading frame	948	57.5	1,141	65.9	<.0001
	In-Frame Deletion (IFD)	Small deletions, splice site mutations or large genomic rearrangements that result in a change in the mRNA but do not change the open reading frame	1	<0.1	2	0.1	.518
	Missense (MS)	Results in an altered amino acid	46	2.8	13	0.8	.0001
	Nonsense (NS)	Point mutation resulting in a stop codon	313	19.0	380	22.0	.027
	Splice (SP)	Results in aberrant RNA splicing	166	10.1	131	7.6	.013
	Multiple Types (including those listed above)		20	1.1	19	1.1	1.00
Mutation Effect	No RNA	Mutation is predicted to abrogate RNA production	21	1.3	6	0.3	.003
	Premature Termination Codon (PTC)	Result of a nonsense substitution, frameshift due to small deletion or insertion, aberrant splicing, or large genomic rearrangement	1,331	81.0	1,542	89.0	<.0001
	Unknown/Other	Unknown effect	298	18.0	183	10.6	<.0001
Mutation Function	Nonsense-Mediated Decay (NMD)[a] (Anczukow et al., 2008)	Mutation is predicted to result in reduced transcript level due to decay of RNA and/or degradation/instability of truncated proteins	1,213	73.9	1,523	88.0	<.0001
	No NMD	Mutations generating a premature stop codon in the first or last exon that is predicted not to result in NMD	58	3.5	16	0.9	<.0001
	No RNA	Loss of expression due to deletion of promoter and/or transcription start site	21	1.3	6	0.4	.003
	Re-Initiation	Mutations presumed to result in translation re-initiation but produce unstable protein	4	0.2	0	0.0	.294
	NMD/Re-initiation	Mutations presumed to result in translation re-initiation but produce unstable protein	60	3.7	0	0.0	–
	Unknown/Other	Unknown function	294	17.8	187	10.7	<.0001
Mutation Class	1	Mutations predicted to be associated with unstable or no protein	1,298	78.6	1,529	88.3	<.0001
	2	Mutations predicted to be associated with stable mutant proteins	112	6.8	36	2.1	<.0001
	3	Unknown function	240	14.6	167	9.6	<.0001

P-values reflect the comparison of frequencies between *BRCA1* and *BRCA2* mutation carriers.
[a]References (Anczukow et al., 2008; Buisson, et al., 2006; Mikaelsdottir, et al., 2004; Perrin-Vidoz, et al., 2002; Ware, et al., 2006)

only tested for the three founder mutations, this number is likely to be underestimated.

In African Americans, the majority of *BRCA1* mutations were not observed in any other racial/ethnic group, implying these mutations may be of African origin. In Hispanics, the most common *BRCA1* mutations also were observed among individuals from other regions who did not self-identify as Hispanic, including *BRCA1* c.3331_3334del (also observed in Australia, Europe, USA, and the UK), and *BRCA1* c.68_69del (the Jewish founder mutation) (Weitzel et al., 2005, 2013). The *BRCA1* c.815_824dup mutation has been reported as being of African origin, but has also been reported as a recurrent mutation in Mexican Americans, perhaps as a reflection of the complex continental admixture of this population (Villarreal-Garza et al., 2015b). *BRCA1* c.390C > A and c.5496_5506delinsA were most commonly found in the Asian population. In *BRCA2*, c.2808_2811del was found among the 10 most frequent mutations in all races/ethnicities.

3.4 | Recurrent mutations

As expected, the most common mutations in the entire data set were the founder mutations *BRCA1* c.5266dup (5382insC), *BRCA1* c.68_69del (185delAG), and *BRCA2* c.5946del (6174delT). In part, the

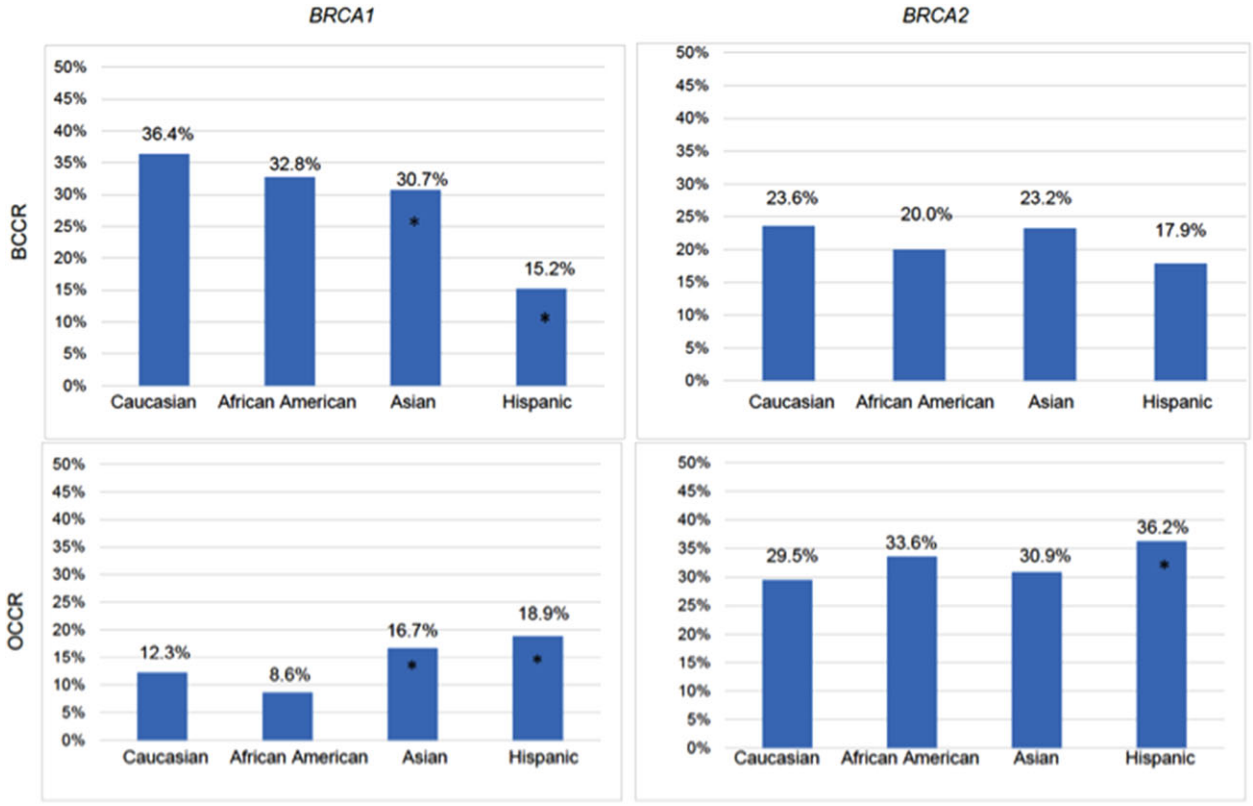


FIGURE 2 Proportion of mutations in the breast cancer cluster regions (BCCR) and ovarian cancer cluster region (OCCR) in BRCA1 and BRCA2 by ethnicity as defined previously (Rebbeck et al., 2015). Asterisk indicates proportion is significantly different than Caucasian proportion (p-value < 0.05)

high frequency of these mutations is a consequence of panels that facilitate testing for these three mutations in women of Jewish descent. However, these two *BRCA1* mutations also are relatively common in regions with a low proportion of individuals who self-identify as Jewish (e.g., Hungary, Czech Republic, France, Germany, Italy, Poland Spain, Russia, and UK). *BRCA1* c.5266dup is a founder mutation thought to have originated 1800 years ago in Scandinavia/Northern Russia, entering the Ashkenazi-Jewish population 400–500 years ago, and thus has origins and a spread pattern independent of the Ashkenazim (Hamel et al., 2011). Haplotype studies have been used to determine the origin of *BRCA1* c.68_69del in populations not considered to have a high proportion of Jewish ancestry. In some populations, such as the Hispanics in the USA and Latin American, it is associated with the Ashkenazi Jewish haplotype, presumably due to unrecognized (Jewish) ancestry (Ah Mew, Hamel, Galvez, Al-Saffar, & Foulkes, 2002; Velez et al., 2012; Weitzel et al., 2005). In other populations, such as Pakistani and Malaysians, where *BRCA1* c.68_69del is a recurrent mutation, it appears to have arisen independently, as it is carried on a distinct haplotype (Kadalmani et al., 2007; Rashid et al., 2006). A different haplotype was also reported for several British families (the 'Yorkshire haplotype') that is distinct from both the Jewish and the Indian-Pakistani haplotypes (Laitman et al., 2013; Neuhausen et al., 1996).

The only locations in which these three founder mutations were not commonly observed were Belgium and Iceland. Iceland has another founder mutation (i.e., *BRCA2* c.771_775del). Yet other founder mutations included *BRCA1* c.4327C > T and *BRCA2* c.8537_8538del in Quebec. This latter mutation in *BRCA2* also is the most common mutation in high-risk families in Sardinia (Pisano et al., 2000) and was also reported in a few Jewish Yemenite families, with a distinct haplotype(Palomba et al., 2007). The *BRCA1* c.181T > G mutation was observed in Central Europe (Austria, Czech Republic, Germany, Hungary, Italy and Poland), but also observed in the US, Argentina, Latvia, Lithuania and Israel. This mutation has been found on a common haplotype in individuals of Polish and Ashkenazi Jewish ancestry, suggesting it is an Eastern European founder mutation (Kaufman, Laitman, Gronwald, Lubinski, & Friedman, 2009). The large rearrangement mutation in *BRCA1* c.548-?_4185+?del (ex9-12del) appears to be an important founder mutation in Mexico, with findings of a common haplotype and an estimated age at 74 generations (~1,500 years) (Weitzel et al., 2013).

We observed a number of other recurrent mutations. *BRCA1* c.3331_3334del comprised more than half of all mutations identified in Colombia, consistent with a previous report that this is a founder mutation in the Colombian population (Torres et al., 2007). However, this mutation has not been found at high rates in a second Colombian population (Cock-Rada, et al., 2017). *BRCA2* c.2808_2811del was frequently observed, not only as the most common mutation in France and Colombia, but also in other Western and Southern European countries, and destinations to which individuals from these countries have migrated. It estimated to have arisen approximately 80 (46–134)

TABLE 2 Common *BRCA1* mutations by country of origin (by family)

Conti-nent	Country	Families	Unique mutations	Five most common mutations (number observed)				
				1	2	3	4	5
Africa	Nigeria	20	15	c.303T > G(4)	c.191G > A(2)	c.3268C > T(2)	c.4240dup(1)	c.4122_4123del(1)
	South Africa	49	16	c.2641G >T(18)	c.5266dup(7)	c.1374del(4)	c.68_69del(4)	c.3228_3229del(4)
Asia	Hong Kong	70	45	c.470_471del(7)	c.4372C > T(5)	c.2635G > T(4)	c.5406+1_5406+3del(4)	c.3342_3345del(4)
	Israel	679	7	c.68_69del(510)	c.5266dup(151)	c.2934T > G(13)	c.181T > G(2)	c.981_982del(1)
	Korea	158	61	c.390C > A(19)	c.5496_5506delinsA(17)	c.922_924delinsT(11)	c.5030_5033del(9)	c.3627dup(8)
	Malaysia	72	47	c.2635G > T(5)	c.68_69del (4)	c.470_471del(3)	c.4148C > G(3)	c.3770_3771del(3)
	Pakistan	93	45	c.5503C > T(11)	c. 3770_3771del(8)	c.4508C > A(8)	c.66dup(6)	c.2269del(1)
	Singapore	28	18	c.2726dup(9)	c.2617dup(2)	c.2635G > T(2)	c.213-12A > G(1)	c.3214del(1)
	Turkey	1	1	c.3333del(1)				
Australia	Australia	581	173	c.68_69del(56)	c.5266dup(45)	c.4065_4068del (23)	c.3756_3759del (22)	c.5503C > T(16)
Europe	Albania	1	1	c.4225C > T (1)				
Europe	Austria	391	115	c.181T > G(51)	c.5266dup(46)	c.3018_3021del(35)	c.1687C > T(26)	c.962G > A(17)
	Belgium	166	41	c.2359dup(40)	c.212+3A > G(26)	c.3661G > T(12)	c.3607C > T(10)	c.3841C > T(9)
	Bosnia	1	1	c.4158_4162del(1)				
	Czech Rep.	208	42	c.5266dup(87)	c.3700_3704del(25)	c.181T > G(20)	c.1687C > T(16)	c.3756_3759del(6)
	Denmark	667	101	c.2475del(91)	c.3319G > T(81)	c.5266dup(41)	c.3710del(39)	c.5213G > A(30)
	Finland	57	31	c.3485del(8)	c.4097-2A > G (5)	c 5266dup(4)	c.1687C > (T42)	c.4327C > T(3)
	France	1,522	418	c.5266dup(118)	c.3481_3491del(70)	c.68_69del(63)	c.4327C > T(49)	c.3839_3843delins AGGC (40)
	Germany	2,287	381	c.5266dup(411)	c.181T > G(196)	c.4689C > G(63)	c.1687C > T(62)	c.3481_3491del(55)
	Greece	208	41	c.5266dup(47)	c.5212G > A(29)	c.5406+644_*8273del(24)	c.5468-285_5592+ 4019del insCACAG(23)	c.5251C > T(13)
	Hungary	235	47	c.5266dup(78)	c.181T > G(60)	c.68_69del(22)	c.5278-?_5406+?del(5)	c.5251C > T(4)
	Iceland	3	1	c.5074G > A(3)				
	Ireland	2	2	c.547+1G > T(1)	c.427G > T(1)			
	Italy	1,120	254	c.5266dup(124)	c.181T > G(44)	c.190T > C(43)	c.1687C > T(39)	c.1380dup(37)
	Latvia	100	9	c.5266dup(49)	c.4035del(40)	c.181T > G(5)	c.3756_3759del(1)	c.4675G > A(1)
	Lithuania	223	21	c.4035del(112)	c.5266dup(58)	c.181T > G221)	c.1687C > T(5)	c.5177_5180del(4)
	Netherlands	782	126	c.5333-36_5406+ 400del(87)	c.5277+1G > A(66)	c.2685_2686del(60)	c.2197_2201del(41)	c.5266dup(40)

(Continues)

TABLE 2 (Continued)

Conti-nent	Country	Families	Unique mutations	Five most common mutations (number observed)				
				1	2	3	4	5
	Poland	1,064	8	c.5266dup(711)	c.181T > G(276)	c.4035del(69)	c.5333-36_5406+400del(3)	c.68_69del(2)
	Portugal	49	23	c.3331_3334del(15)	c.2037delinsCC(7)	c.3817C > T(3)	c.21A > G(2)	c.5266dup(2)
	Romania	1	1	c.5266dup(1)				
	Russia	160	10	c.5266dup(135)	c.4035del(11)	c.68_69del(7)	c.5026_5027del(1)	c.4185+2T > C(1)
	Spain	678	181	c.211A > G(78)	c.68_69del(62)	c.5123C > A(61)	c.3770_3771del(23)	c.3331_3334del(23)
	Sweden	438	108	c.3048_3052dup(68)	c.1687C > T(31)	c.2475del(27)	c.1082_1092del(26)	c.5266dup(19)
	UK	1,389	297	c.68_69del(134)	c.4065_4068del(104)	c.4186-?_4357+?dup (78)	c.3756_3759del(62)	c.5266dup(60)
North America	Canada	450	112	c.68_69del(99)	c.4327C > T(66)	c.5266dup(50)	c.2834_2836delinsC(16)	c.3756_3759del(12)
	USA	4,219	613	c.68_69del(1130)	c.5266dup(554)	c.3756_3759del(113)	c.4065_4068del(58)	c.3756_3759(49)
	Argentina	89	35	c.68_69del(22)	c.5266dup(12)	c.211A > G(11)	c.181T > G(6)	c.427G > T(3)
South/ Central America	Brazil	101	39	c.5266dup(31)	c.3331_3334del(18)	c.135-?_441+?del(4)	c.1687C > T(4)	c.3916_3917del(3)
	Colombia	55	2	c.3331_3334del(36)	c.5123C > A(19)			
	Mexico	25	15	c.548-?_4185+?del(8)	c.68_69del(2)	c.824_825ins10(2)	c.211A > G(2)	c.5030_5033del(1)
	Peru	1	1	c.4986+6T > C(1)				
	Venezuela	1	1	c.5123C > A(1)				

TABLE 3 Frequently observed *BRCA2* mutations by country of origin (by family)

Conti-nent	Country	Families	Unique mutations	Five most frequently observed mutations (number observed)				
				1	2	3	4	5
Africa	Nigeria	12	9	c.1310_1313del(3)	c.8817_8820delA(2)	c.5241_5242insTA(1)	c.2402_2412del(1)	c.994del(1)
	South Africa	103	18	c.7934del(80)	c.5946del(6)	c.6944_6947del(2)	c.5213_5216del(1)	c.6939del(1)
Asia	Hong Kong	91	45	c.3109C > T(22)	c.2808_2811del(5)	c.7878G > A(5)	c.7007G > T(4)	c.9294C > G(4)
	Israel	339	5	c.5946del(330)	c.8537_8538del(5)	c.4936_4939del(2)	c.3847_3848del(1)	c.6024dup(1)
	Japan	1	1	c.5645C > A(1)				
	Korea	220	93	c.7480C > T(40)	c.3744_3747del(18)	c.1399A > T(16)	c.5576_5579del(14)	c.6724_6725del(6)
	Malaysia	64	47	c.262_263del(8)	c.2808_2811del(3)	c.3109C > T(3)	c.5073dup(3)	c.809C > G(2)
	Pakistan	19	17	c.5222_5225del(3)	c.8754+1G > T(1)	c.92G > A(1)	c.6468_6469del(1)	c.2990T > G(1)
	Philippines	1	1	c.2023del(1)				
	Qatar	1	1	c.7977-1G > C(1)				
	Saudi Arabia	1	1	c.473C > A(1)				
	Singapore	10	10	c.200_1910-877dup(1)	c.2808_2811del(1)	c.8961_8964del(1)	c.8915del(1)	c.956dup(1)
Australia	Australia	496	178	c.5946del(53)	c.6275_6276del(25)	c.7977-1G > C(11)	c.5682C > G(10)	c.3487_3848del(10)
Europe	Austria	185	87	c.8364G > A(17)	c.8755-1G > A(15)	c.3860del(11)	c.1813dup(8)	c.7846del(6)
	Belgium	116	39	c.6275_6276del(17)	c.516+1G > T(16)	c.8904del(14)	c.1389_1390del(9)	c.3847_3848del(7)
	Czech Republic.	81	42	c.8537_8538del(12)	c.7913_7917del(5)	c.5645C > A(4)	c.2808_2811del(4)	c.9403del(4)
	Denmark	442	101	c.7617+1G > A(61)	c.6373del(44)	c.1310_1313del (25)	c.6486_6489del(25)	c.3847_3848del(16)
	Finland	52	16	c.9118-2A > G(18)	c.7480C > T(12)	c.771_775del(7)	c.8327T > G(2)	c.1286T > G(2)
	France	997	375	c.2808_2811del(34)	c.5946del(27)	c.9026_9030del(22)	c.8364G > A(22)	c.5909C > A(19)
	Germany	1,109	367	c.1813dup(51)	c.3847_3848del(34)	c.2808_2811del(29)	c.5946del(29)	c.5682C > G(23)
	Greece	28	22	c.7976G > A(3)	c.5722_5723del(2)	c.9097dup(2)	c.9501+1G > A(2)	c.5722_5723del(2)
	Hungary	81	39	c.9097dup(17)	c.5946del(11)	c. 7913_7917del(4)	c.6656C > G(3)	c.9403del(3)
	Iceland	89	1	c.771_775del(89)				
	Ireland	2	2	c.8951C > G(1)	c.5576_5579del(1)			
	Italy	706	242	c.8878C > T(33)	c.6468_6469del(31)	c.7180A > T(29)	c.5682C > G(25)	c.8247_8248delGA(18)
	Lithuania	26	11	c.658_659del(13)	c.3847_3848del(4)	c.6580dup(1)	c.6410del(1)	c.7879A > T(1)
	Netherlands	493	167	c.6275_6276del(38)	c.8067T > A(26)	c.5946del(25)	c.9672dupA(23)	c. 5213_5216del (21)

(Continues)

TABLE 3 (Continued)

Conti-nent	Country	Families	Unique mutations	Five most frequently observed mutations (number observed)				
				1	2	3	4	5
	Norway	2	1	c.771_775del(2)				
	Poland	23	20	c.5946del(3)	c.8946del(2)	c. 7913_7917del(1)	c.9294C > A(1)	c.635_636del(1)
	Portugal	71	22	c.156_157insAlu(39)	c.9097dup(5)	c.9382C > T(3)	c.682-2A > C(2)	c.5645G > A(2)
	Romania	1	1	c.9097dup(1)				
	Russia	3	3	c.3682_3685del(1)	c.5410_5411del(1)	c.5946del(1)		
	Spain	670	217	c.3264dup(58)	c.2808_2811del(56)	c.9026_9030del(52)	c.6275_6276del(32)	c.9018C > A(16)
	Sweden	123	68	c.4258del(11)	c.2830A > T(7)	c.1796_1800del(6)	c.3847_3848del(6)	c.7558C > T(5)
	UK	1,200	308	c.6275_6276del(107)	c.5946del(66)	c.4478_4481del(37)	c.755_758del(36)	c.5682C > G(33)
North America	Canada	311	108	c.8537_8538del(48)	c.5946del(45)	c.2808_2811del(13)	c.6275_6276del(11)	c.5857G > T(10)
	USA	3,064	626	c.5946del(742)	c.2808_2811del(86)	c.1813dup(62)	c.658_659del(50)	c.6275_6276del(49)
	Argentina	49	21	c.5946del(18)	c.2808_2811del(5)	c.6037A > T(4)	c.9026_9030del(2)	c.5645C > G(2)
	Brazil	47	33	c.2T > G(5)	c.2808_2811del(4)	c.156_157insAlu(4)	c.6405_6409del(3)	c.1138del(2)
South/ Central America	Colombia	19	4	c.2808_2811del(15)	c.5851_5854del (2)	c.6275_6276del(1)	c.93G > A(1)	
	Costa Rica	1	1	c.9235del(1)				
	Honduras	1	1	c.7558C > T(1)				
	Mexico	6	6	c.3264dup (1)	c.6275_6276del (1)	c.2224C > T (1)	c.5542del (1)	c.6502G > T (1)

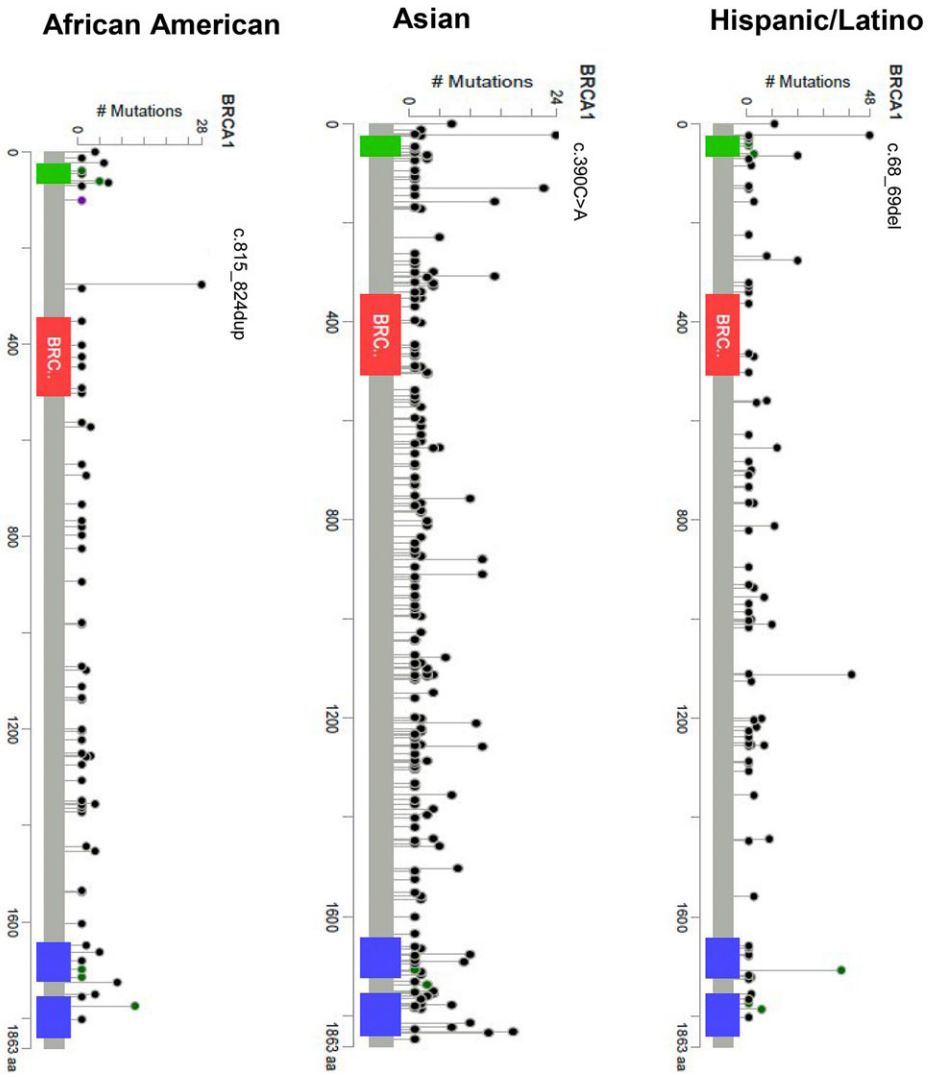


FIGURE 3 *BRCA1* mutation distribution in African American, Asian, and Hispanic. Length of mutation indicator reflects the number of observed mutations. Domains are zinc/ring finger (green); BRCT domain (red); BRCT (C terminus) (blue). Mutation type is indicated for each mutation by color: green: missense mutations; black: truncating mutations (nonsense, nonstop, frameshift deletion, frameshift insertion, splice site, in-frame mutations); purple: all other types of mutations

generations ago. However, due to the diversity of the haplotypes, multiple independent origins could not be ruled out (Neuhausen et al., 1998). *BRCA2* c.6275_6276del was a recurrent *BRCA2* mutation in Australia, the UK, Belgium, Spain, the Netherlands, and North America. This mutation has been estimated to have originated 52 (24–98) generations ago from a single founder (Neuhausen et al., 1998). Recurrent or founder mutations were observed in diverse populations. For example, the c.115T > G (Cys39Gly) mutation has been described in Greenlanders (Hansen et al., 2009). The c.2641G>T and c.7934del mutations have both been reported as founder mutation in South African Afrikaners (Reeves et al., 2004).

4 | DISCUSSION

We have reported worldwide distribution of *BRCA1* and *BRCA2* mutations curated in the CIMBA dataset. These results may aid in the understanding of the mutation distribution in specific populations as well as imparting clinical and biological implications for our understanding of *BRCA1*- and *BRCA2*-associated carcinogenesis.

Clinical testing for *BRCA1* and *BRCA2* mutations has benefited substantially from knowledge about common mutations in specific populations. In many countries, the three Ashkenazi-Jewish founder mutations are offered as a mutation testing panel for self-reported Ashkenazim, based on their frequency. This approach is much less expensive than comprehensive gene sequencing. The identification of commonly-occurring mutations in other populations could lead to more efficient and cost-effective mutation testing for *BRCA1* and *BRCA2*. For example, Villareal-Garza et al. (2015a) have developed the HISPANEL of mutations that optimizes testing in Hispanic/Latino populations. In the present study, we have identified mutations that may exist at a sufficient prevalence to warrant consideration for population-specific mutation testing panels. Criteria for developing such panels for *BRCA1* and *BRCA2* mutation screening are not available. However, mutations that are in a specific population and that capture a sufficient

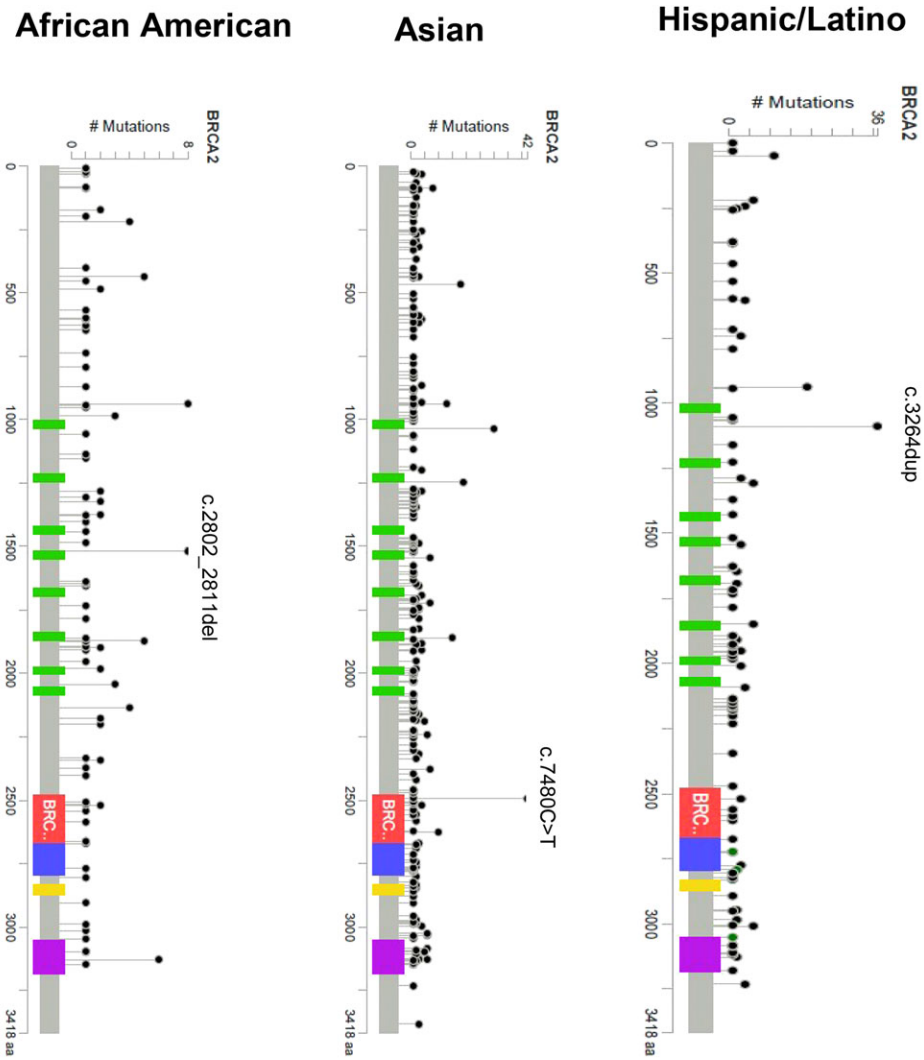


FIGURE 4 *BRCA2* mutation distribution in African American, Asian, and Hispanic CIMBA sample (per family). Length of mutation indicator reflects the number of observed mutations. Domains are BRCA repeats (green); BRCA helica (red); OB binding domain (blue); tower (yellow) and OB3 binding domain (purple). Mutation type is indicated for each mutation by color: green: missense mutations; black: truncating mutations (nonsense, nonstop, frameshift deletion, frameshift insertion, splice site, in-frame mutations); purple: all other types of mutations

percentage of mutations in high risk individuals and families in that population may be appropriate for use in targeted genetic testing. Before such panels can be developed, population-based studies of mutation frequency in specific populations should be undertaken. The data reported herein provide a list of the recurrent mutations around which such panels could be developed, but the frequencies are not population based, particularly in settings where founder mutations are preferentially screened (e.g., the Jewish founder panels). Similarly, putative founder mutations identified by assessing common ancestral origins of specific mutations (rather than just high prevalence; Table 5) may form the basis of population-specific *BRCA1* and *BRCA2* mutation screening panels.

We report the distribution of *BRCA1* and *BRCA2* mutations in nearly 30,000 families of bona-fide disease-associated mutations. The strengths of this report include the large sample size that reflects a geographically and racially/ethnically diverse set of *BRCA1* and *BRCA2* mutation carriers. However, some limitations need to be considered. First, the sample set presented here does not reflect a systematic study of these populations or races/ethnicities; the data reflect patterns of recruitment (e.g., individuals with higher risk or prior diagnosis of cancer who consented to participate in research protocols) that contributed to the CIMBA consortium. Certain racial/ethnic or sociodemographic groups are under- or overrepresented or missing in our data set and, as a consequence, mutations may be over- or underrepresented. For example, the existence of a commercial panel of three Jewish founder mutations enhances genetic testing for those mutations. As a result, the most frequently observed mutations in some populations (e.g., the United States) reflect the widespread use of this testing panel in the US population. Similar arguments may also apply for other populations, where testing for certain founder mutations may be more frequent. Therefore, the relative frequencies of mutations by population in the present study may be subject to such testing biases. Comparing the relative frequencies is also complicated by the inclusion of related individuals.

Second, although the CIMBA data represent most regions around the world, there are limitations related to which groups of

TABLE 4 Ten most frequently observed mutations by self-identified race/ethnicity (%) (by family)

	Mutation rank	Caucasian	African American	Asian	Hispanic/Latino	Jewish	Other
BRCA1	1	c.5266dup(17%)	c.815_824dup(16%)	c.390C > A(4%)	c.68_69del(12%)	c.68_69del(72%)	c.5266dup(12%)
	2	c.181T > G (6%)	c.5324T > G (7%)	c.5496_5506delinsA (3%)	c.3331_3334del(10%)	c.5266dup(24%)	c.68_69del(17%)
	3	c.68_69del(6%)	c.5177_5180del(5%)	c.470_471del(3%)	c.5123C > A(9%)	c.3756_3759del (0.3%)	c.181T > G(5%)
	4	c.4035del(2%)	c.4357+1G > A(5%)	c.5503C > T(2%)	c.548-?_4185+?del(7%)	c.1757del(0.3%)	c.5333-36_5406+400del(3%)
	5	c.4065_4068del(2%)	c.190T > G(3%)	c.922_924delinsT(2%)	c.211A > G(5%)	c.2934T > G(0.2%)	c.3481_3491del(2%)
	6	c.3756_3759del(2%)	c.68_69del(3%)	c.68_69del(2%)	c.815_824del(3%)	c.5503C > T(0.1%)	c.1687C > T (2%)
	7	c.1687C > T(2%)	c.5467+1G > A(3%)	c.3770_3771del(2%)	c.2433del(3%)	c.4185+1G > T(0.1%)	c.4065_4068del(2%)
	8	c.4327C > T(2%)	c.182G > A(3%)	c.2635G > T(2%)	c.1960A > T(3%)	c.4689C > G(0.1%)	c.5277+1G > A (2%)
	9	c.2475del(2%)	c.5251C > T(2%)	c.2726dup(2%)	c.3029_3030del(3%)	c.3770_3771del (0.1%)	c.2685_2686del(68%)
	10	c.4186-?_4357+?dup(1%)	c.4484G > T(2%)	c.3627dup(2%)	c.4327C > T(2%)	c.4936del(0.1%)	c.4327C > T(1%)
Families		11,258	174	550	408	1,852	4,583
Unique Mutations		1,206	77	240	104	56	765
BRCA2	1	c.5946del(5%)	c.2808_2811del(6%)	c.7480C > T(8%)	c.3264dup(17%)	c.5946del(94%)	c.5946del(5%)
	2	c.6275_6276del(3%)	c.4552del(6%)	c.3109C > T(6%)	c.2808_2811del(9%)	c.3847_3848del (0.4%)	c.6275_6276del(4%)
	3	c.2808_2811del(3%)	c.9382C > T(5%)	c.3744_3747del(4%)	c.145G > T(5%)	c.1754del(0.4%)	c.2808_2811del(3%)
	4	c.771_775del(2%)	c.1310_1313del(4%)	c.1399A > T(3%)	c.9026_9030del(3%)	c.9382C > T(0.3%)	c.1813dup(3%)
	5	c.3847_3848del(2%)	c.5616_5620del(4%)	c.5576_5579del(3%)	c.658_659del(3%)	c.5621_5624del (0.2%)	c.5645C > A(2%)
	6	c.5682C > G(2%)	c.6405_6409del(3%)	c.2808_2811del(2%)	c.5542del(3%)	c.2808_2811del (0.2%)	c.1310_1313del(2%)
	7	c.1813dup(2%)	c.658_659del(3%)	c.7878G > A(2%)	c.3922G > T(3%)	c.4829_4830del (0.2%)	c.3847_3848del(2%)
	8	c.8537_8538del(1%)	c.2957_2958insG(2%)	c.262_263del(2%)	c.1813dup(2%)	c.5238del(0.2%)	c.5682C > G(1%)
	9	c.658_659del(1%)	c.7024C > T(2%)	c.7133C > G(1%)	c.9699_9702del(2%)	c.9207T > A(0.1%)	c.9672dup(1%)
	10	c.7934del(1%)	c.6531_6534del(2%)	c.5164_5165del(1%)	c.6275_6276del(2%)	c.3264dup(0.1%)	c.658_659del(1%)
Families		7,156	125	538	207	990	2,551
Unique Mutations		1,242	77	248	91	44	753

TABLE 5 Ten most frequently observed mutations by continent of ascertainment (%) (by family)

	Mutation rank	North America	Africa	Asia	South/Central America	Europe	Australia
BRCA1	1	c.68_69del(26%)	c.2641G >T(26%)	c.68_69del(47%)	c.3331_3334del (20%)	c.5266dup(17%)	c.68_69del(10%)
	2	c.5266dup(13%)	c.5266dup(10%)	c.5266dup(14%)	c.5266dup(16%)	c.181T > G(7%)	c.5266dup(8%)
	3	c.181T > G(3%)	c.1374del(6%)	c.390C > A(2%)	c.68_69del(9%)	c.68_69del(4%)	c.4065_4068del(4%)
	4	c.4327C > T(2%)	c.68_69del(6%)	c.5496_5506delinsA (2%)	c.5123C > A(8%)	c.4035del(2%)	c.3756_3759del(4%)
	5	c.4065_4068del(1%)	c.3228_3229del(6%)	c.5503C > T(1%)	c.211A > G(5%)	c.1687C > T(2%)	c.5503C > T(3%)
	6	c.3756_3759del(1%)	c.303T > G(6%)	c.2934T > G(1%)	c.181T > G(3%)	c.4065_4068del(2%)	c.4186-?_4357+?dup(3%)
	7	c.213-11T > G(1%)	c.4838_4839insC (3%)	c.3770_3771del(1%)	c.548-?_4183+8?del(3%)	c.3481_3491del(1%)	c.4327C > T(2%)
	8	c.1687C > T(1%)	c.3268C > T(3%)	c.2726dup(1%)	c.1687C > T(2%)	c.2475del(1%)	c.5278-?_5592+?del (2%)
	9	c.4186-?_4357+?dup(1%)	c.1504_1508del(3%)	c.470_471del(1%)	c.135-?_441+?del(2%)	c.3756_3759del(1%)	c.70_80del(2%)
	10	c.1175_1214del(1%)	c.191G > A(3%)	c.922_924delinsT(1%)	c.5030_5033del (2%)	c.3770_3704del(1%)	c.1961del(2%)
Families		4,669	69	1,100	271	11,748	581
Unique Mutations		654	30	187	75	1282	173
BRCA2	1	c.5946del(23%)	c.7934del(47%)	c.5946del(34%)	c.2808_2811del (11%)	c.6275_6276del(2%)	c.5946del(5%)
	2	c.2808_2811del(3%)	c.5946del(4%)	c.7480C > T(4%)	c.5946del(9%)	c.5946del(2%)	c.6275_6276del(2%)
	3	c.8537_8538del(2%)	c.1310_1313del(2%)	c.3109C > T(3%)	c.2T > G(2%)	c.2808_2811del(2%)	c.7977-1G > C(1%)
	4	c.1813dup(2%)	c.6944_6947del(1%)	c.3744_3747del(2%)	c.156_157insAlu (2%)	c.771_775del(1%)	c.5682C > G(1%)
	5	c.6275_6276del(2%)	c.8817_8820del(1%)	c.1399A > T(2%)	c.6037A > T(2%)	c.3847_3848del(1%)	c.3847_3848del(1%)
	6	c.3847_3848del(3%)	c.5213_5216del(1%)	c.5576_5579del(2%)	c.6405_6409del(3%)	c.1813dup(1%)	c.2808_2811del(1%)
	7	c.658_659del(2%)	c.6535_6536insA (1%)	c.2808_2811del(1%)	c.5645C > G(1%)	c.5682C > G(1%)	c.755_758del(1%)
	8	c.9382C > T(1%)	c.774_775del(1%)	c.262_263del(1%)	c.658_659del(1%)	c.1310_1313del(1%)	c.4478_4481del(1%)
	9	c.3264dup(1%)	c.6393del(1%)	c.8537_8538del(1%)	c.7180A > T(1%)	c.5645C > A(1%)	c.8297del(1%)
	10	c.55073dup(1%)	c.5042_5043del(1%)	c.7878G > A(1%)	c.5851_5854del (1%)	c.9026_9030del(1%)	c.250C > T(1%)
Families		3,375	170	976	222	10,175	1,047
Unique Mutations	660	27	187	58	1,315	179	

individuals have been tested and which centers contributed data. In particular, non-White ancestry populations are still underrepresented in research reports of mutation spectrum and frequency. Genetic testing in the developing world remains limited.

Third, we presented the mutations in terms of type or effect (Table 1), but these designations are not always based on experimental evidence. For example, NMD mutation status is almost always defined by a prediction rule rather than in vitro experiments that confirm the presence of nonsense mediated decay.

Fourth, we presented the occurrence of putative founder mutations. Some of these founder mutations (e.g., *BRCA1* c.68_69del, *BRCA2* c.771_775del) have been demonstrated to be true founder mutations based on actual ancestry analyses. Others, however, have only been identified as occurring commonly in certain populations, but haplotype or similar analyses of founder status may not have been done.

Fifth, our analysis was based on self-reported race/ethnicity of study participants, but this information may misclassify some groups of individuals. For example, some Middle Eastern groups may have been classified as "Caucasian" based on the data available, but in fact may represent a distinct group that was not captured here. Moreover, in some large centers participating in CIMBA, collecting information on race/ethnicity is prohibited and these mutation carriers were excluded from the comparisons.

Finally, we evaluated mutations by racial/ethnic and geographic designations, but some of these may be misclassified. For example, while *BRCA1* c.68_69del has been shown to arise independently of the Jewish founder mutation in Pakistan (Rashid et al., 2006), we cannot determine if the identified group also contains some Ashkenazi Jewish individuals.

The data presented herein provide new insights into the worldwide distribution of *BRCA1* and *BRCA2* mutations. The identification of recurrent mutations in some racial/ethnic groups or geographical locations raises the possibility of defining more efficient strategies for genetic testing. Three Jewish founder mutations *BRCA1* c.5266dup (5382insC) and *BRCA1* c.68_69del (185delAG) and *BRCA2* c.5946del (6174delT) have long been used as a primary genetic screening test for women of Jewish descent. The identification here of other recurrent mutations in specific populations may similarly provide the basis for other mutation-specific panels. For example, *BRCA1* c.5266dup (5382insC) may be useful as a single mutation screening test in Central-Eastern European populations before undertaking full sequencing. However, this basic test may be supplemented with screening for *BRCA1* c.181T > G, as the second most common mutation of the region, and for some special cases, to include most common Hungarian *BRCA2* founder mutation c.9097dup (9326insA) for those with Hungarian ancestry (Ramus et al., 1997b; van der Looij et al., 2000). In Iceland, only two mutations were reported: the founder mutation *BRCA2* c.771_775del and the rarer *BRCA1* c.5074G > A (Bergthorsson et al., 1998). A number of other situations can be identified in which specific mutations explain a large proportion of the total mutations observed in a population. These and other such examples suggest that targeted mutation testing panels that include specific mutations could be developed for use in specific populations. Finally, we focused on female *BRCA1* and *BRCA2* mutation carriers in this report. However, the growing knowledge about *BRCA1* and *BRCA2*-associated cancers in men, particularly prostate cancer (Ostrander & Udler, 2008; Pritchard et al., 2016), suggests that the information presented herein will also have value in genetic testing of men.

ACKNOWLEDGMENTS

Study	Funding	Acknowledgments
CIMBA	The CIMBA data management and data analysis were supported by Cancer Research – UK grants C12292/A20861, C12292/A11174. ACA is a Cancer Research -UK Senior Cancer Research Fellow. GCT and ABS are NHMRC Research Fellows. iCOGS: the European Community's Seventh Framework Programme under grant agreement n° 223175 (HEALTH-F2-2009-223175) (COGS), Cancer Research UK (C1287/A10118, C1287/A 10710, C12292/A11174, C1281/A12014, C5047/A8384, C5047/A15007, C5047/A10692, C8197/A16565), the National Institutes of Health (CA128978) and Post-Cancer GWAS initiative (1U19 CA148537, 1U19 CA148065 and 1U19 CA148112 - the GAME-ON initiative), the Department of Defence (W81XWH-10-1-0341), the Canadian Institutes of Health Research (CIHR) for the CIHR Team in Familial Risks of Breast Cancer (CRN-87521), and the Ministry of Economic Development, Innovation and Export Trade (PSR-SIIRI-701), Komen Foundation for the Cure, the Breast Cancer Research Foundation, and the Ovarian Cancer Research Fund. The PERSPECTIVE project was supported by the Government of Canada through Genome Canada and the Canadian Institutes of Health Research, the Ministry of Economy, Science and Innovation through Genome Québec, and The Quebec Breast Cancer Foundation.	All the families and clinicians who contribute to the studies; Sue Healey, in particular taking on the task of mutation classification with the late Olga Sinilnikova; Maggie Angelakos, Judi Maskiell, Gillian Dite, Helen Tsimiklis

(Continues)

BCFR - all	This Breast Cancer Family Registry (BCFR) is supported by grant UM1 CA164920 from the USA National Cancer Institute. The content of this manuscript does not necessarily reflect the views or policies of the National Cancer Institute or any of the collaborating centers in the BCFR, nor does mention of trade names, commercial products, or organizations imply endorsement by the USA Government or the BCFR.	
BCFR-AU		Maggie Angelakos, Judi Maskiell, Gillian Dite, Helen Tsimiklis.
BCFR-NY		We wish to thank members and participants in the New York site of the Breast Cancer Family Registry for their contributions to the study.
BCFR-ON		We wish to thank members and participants in the Ontario Familial Breast Cancer Registry for their contributions to the study.
BFBOCC-LT	BFBOCC is partly supported by: Lithuania (BFBOCC-LT): Research Council of Lithuania grant SEN-18/2015	BFBOCC-LT acknowledge Laimonas Griškevičius. BFBOCC-LV acknowledge Drs Janis Eglitis, Anna Krilova and Aivars Stengrevics.
BIDMC	BIDMC is supported by the Breast Cancer Research Foundation	
BMBSA	BRCA-gene mutations and breast cancer in South African women (BMBSA) was supported by grants from the Cancer Association of South Africa (CANSA) to Elizabeth J. van Rensburg	BMBSA wish to thank the families who contribute to the BMBSA study
BRICOH	SLN was partially supported by the Morris and Horowitz Families Endowed Professorship.	
CEMIC	This work is funded by CONICET and Instituto Nacional del Cancer, Ministerio de Salud de la Nacion Argentina (1995/15)	We thank to Florencia Cardoso, Natalia Liria and Pablo Mele in their biospecimen and data management.
CNIO	CNIO study is partially funded by the Spanish Ministry of Health PI16/00440 supported by FEDER funds, the Spanish Ministry of Economy and Competitiveness (MINECO) SAF2014-57680-R and the Spanish Research Network on Rare diseases (CIBERER)	We thank Alicia Barroso, Rosario Alonso and Guillermo Pita for their assistance.
COH-CCGCRN	City of Hope Clinical Cancer Genomics Community Network and the Hereditary Cancer Research Registry, supported in part by the Breast Cancer Research Foundation, by Award Number RC4CA153828 (PI: J. Weitzel) from the National Cancer Institute and the Office of the Director, National Institutes of Health, and by the National Cancer Institute of the National Institutes of Health under Award Number R25CA171998 (PIs: K. Blazer and J. Weitzel). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health	
CONSIT TEAM	Associazione Italiana Ricerca sul Cancro (AIRC; IG2014 no.15547) to P. Radice; Funds from Italian citizens who allocated the 5 × 1000 share of their tax payment in support of the Fondazione IRCCS Istituto Nazionale Tumori, according to Italian laws (INT-Institutional strategic projects '5 × 1000') to S Manoukian; Associazione Italiana per la Ricerca sul Cancro IG17734; Italian Ministry of University and Research, PRIN projects; Istituto Pasteur-Fondazione Cenci Bolognetti to G. Giannini; FiorGen Foundation for Pharmacogenomics to L. Papi; Funds from Italian citizens who allocated the 5 × 1000 share of their tax payment in support of the IRCCS AOU San Martino - IST according to Italian laws (institutional project) to L. Varesco; Associazione Italiana Ricerca sul Cancro (AIRC; IG2015 no.16732) to P. Peterlongo	Bernard Peissel, Milena Mariani and Daniela Zaffaroni of the Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; Davide Bondavalli, Maria Rosaria Calvello and Irene Feroce of the Istituto Europeo di Oncologia, Milan, Italy; Alessandra Viel and Riccardo Dolcetti of the CRO Aviano National Cancer Institute, Aviano (PN), Italy; Francesca Vignolo-Lutati of the University of Turin, Turin, Italy; Gabriele Capone of the University of Florence, Florence, Italy; Laura Ottini of the "Sapienza" University, Rome, Italy; Viviana Gismondi of the IRCCS AOU San Martino – IST, Istituto Nazionale per la Ricerca sul Cancro, Genoa, Italy; Maria Grazia Tibiletti and Daniela Furlan of the Ospedale di Circolo-Università dell'Insubria, Varese, Italy; Antonella Savarese and Aline Martayan of the Istituto Nazionale Tumori Regina Elena, Rome, Italy; Stefania Tommasi and Brunella Pilato of the Istituto Nazionale Tumori "Giovanni Paolo II" - Bari, Italy, and the personnel of the Cogentech Cancer Genetic Test Laboratory, Milan, Italy.
DFCI	This research has been supported by R01-CA08534 and R01-CA102776 to TRR._____	
DEMOKRITOS	This research has been co-financed by the European Union (European Social Fund – ESF) and Greek national funds through the Operational Program "Education and Lifelong Learning" of the National Strategic Reference Framework (NSRF) - Research Funding Program of the General Secretariat for Research & Technology: SYN11_10_19 NBCA. Investing in knowledge society through the European Social Fund._____	

(Continues)

DKFZ	The DKFZ study was supported by the DKFZ and in part by the SKMCH & RC, Lahore, Pakistan and the Pontificia Universidad Javeriana, Bogota, Colombia.	We thank all participants, clinicians, family doctors, researchers, and technicians for their contributions and commitment to the DKFZ study and the collaborating groups in Lahore, Pakistan (Noor Muhammad, Sidra Gull, Seerat Bajwa, Faiz Ali Khan, Humaira Naeemi, Saima Faisal, Asif Loya, Mohammed Aasim Yusuf) and Bogota, Colombia (Ignacio Briceno, Fabian Gil).
EMBRACE	EMBRACE is supported by Cancer Research UK Grants C1287/A10118 and C1287/A11990. D. Gareth Evans and Fiona Lalloo are supported by an NIHR grant to the Biomedical Research Centre, Manchester. The Investigators at The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust are supported by an NIHR grant to the Biomedical Research Centre at The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust. Ros Eeles and Elizabeth Bancroft are supported by Cancer Research UK Grant C5047/A8385. Ros Eeles is also supported by NIHR support to the Biomedical Research Centre at The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust	RE is supported by NIHR support to the Biomedical Research Centre at The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust
FCCC	The authors acknowledge support from The University of Kansas Cancer Center (P30 CA168524) and the Kansas Bioscience Authority Eminent Scholar Program. A.K.G. was funded by 5U01CA113916, R01CA140323, and by the Chancellors Distinguished Chair in Biomedical Sciences Professorship.	We thank Ms. JoEllen Weaver and Dr. Betsy Bove for their technical support.
FPGMX	This work was partially supported by FISPI05/2275 and Mutua Madrileña Foundation (FMMA).	We would like to thank Marta Santamariña, Ana Blanco, Miguel Aguado, Uxía Esperón and Belinda Rodríguez for their contribution with the study.
GC-HBOC	The German Consortium of Hereditary Breast and Ovarian Cancer (GC-HBOC) is supported by the German Cancer Aid (grant no 110837), Rita K. Schmutzler.	The Regensburg HBOC thanks Dr. Ivana Holzhauser and Dr. Ines Schönbuchner for their contributions to the study
GEMO	The study was supported by the Ligue Nationale Contre le Cancer; the Association "Le cancer du sein, parlons-en!" Award; the Canadian Institutes of Health Research for the "CIHR Team in Familial Risks of Breast Cancer" program and the French National Institute of Cancer (INCa).	Genetic Modifiers of Cancer Risk in *BRCA1* or *BRCA2* Mutation Carriers (GEMO) study: National Cancer Genetics Network «UNICANCER Genetic Group», France. We wish to pay a tribute to Olga M. Sinilnikova, who with Dominique Stoppa-Lyonnet initiated and coordinated GEMO until she sadly passed away on the 30th June 2014, and to thank all the GEMO collaborating groups for their contribution to this study. GEMO Collaborating Centers are: Coordinating Centres, Unité Mixte de Génétique Constitutionnelle des Cancers Fréquents, Hospices Civils de Lyon - Centre Léon Bérard, & Equipe «Génétique du cancer du sein», Centre de Recherche en Cancérologie de Lyon: Olga Sinilnikova†, Sylvie Mazoyer, Francesca Damiola, Laure Barjhoux, Carole Verny-Pierre, Mélanie Léone, Nadia Boutry-Kryza, Alain Calender, Sophie Giraud; and Service de Génétique Oncologique, Institut Curie, Paris: Claude Houdayer, Etienne Rouleau, Lisa Golmard, Agnès Collet, Virginie Moncoutier, Muriel Belotti, Camille Elan, Catherine Nogues, Emmanuelle Fourme, Anne-Marie Birot. Institut Gustave Roussy, Villejuif: Brigitte Bressac-de-Paillerets, Olivier Caron, Marine Guillaud-Bataille. Centre Jean Perrin, Clermont–Ferrand: Yves-Jean Bignon, Nancy Uhrhammer. Centre Léon Bérard, Lyon: Christine Lasset, Valérie Bonadona, Sandrine Handallou. Centre François Baclesse, Caen: Agnès Hardouin, Pascaline Berthet, Dominique Vaur, Laurent Castera. Institut Paoli Calmettes, Marseille: Hagay Sobol, Violaine Bourdon, Tetsuro Noguchi, Audrey Remenieras, François Eisinger. CHU Arnaud-de-Villeneuve, Montpellier: Isabelle Coupier, Pascal Pujol. Centre Oscar Lambret, Lille: Jean-Philippe Peyrat, Joëlle Fournier, Françoise Révillion, Philippe Vennin†, Claude Adenis. Centre Paul Strauss, Strasbourg: Danièle Muller, Jean-Pierre Fricker. Institut Bergonié, Bordeaux: Emmanuelle Barouk-Simonet, Françoise Bonnet, Virginie Bubien, Nicolas Sevenet, Michel Longy. Institut Claudius Regaud, Toulouse: Christine Toulas, Rosine Guimbaud, Laurence Gladieff, Viviane Feillel. CHU Grenoble: Dominique Leroux, Hélène Dreyfus, Christine Rebischung, Magalie Peysselon. CHU Dijon: Fanny Coron, Laurence Faivre. CHU St-Etienne: Fabienne Prieur, Marine Lebrun, Caroline Kientz. Hôtel Dieu Centre Hospitalier, Chambéry: Sandra Fert Ferrer. Centre Antoine Lacassagne, Nice: Marc Frénay. CHU Limoges: Laurence Vénat-Bouvet. CHU Nantes: Capucine Delnatte. CHU Bretonneau, Tours: Isabelle Mortemousque. Groupe Hospitalier Pitié-Salpétrière, Paris: Florence Coulet, Chrystelle Colas, Florent Soubrier, Mathilde Warcoin. CHU Vandoeuvre-les-Nancy: Johanna Sokolowska, Myriam Bronner. CHU Besançon: Marie-Agnès Collonge-Rame, Alexandre Damette. Creighton University, Omaha, USA: Henry T. Lynch, Carrie L. Snyder.

(Continues)

GEORGETOWN	CI received support from the Non-Therapeutic Subject Registry Shared Resource at Georgetown University (NIH/NCI grant P30-CA051008), the Fisher Center for Familial Cancer Research, and Swing Fore the Cure.	
HCBARRETOS	This study was supported by Barretos Cancer Hospital, FINEP - CT-INFRA (02/2010) and FAPESP (2013/24633-2).	We wish to thank members of the Center of Molecular Diagnosis, Oncogenetics Department and Molecular Oncology Research Center of Barretos Cancer Hospital for their contributions to the study.
G-FAST	Bruce Poppe is a senior clinical investigator of FWO. Mattias Van Heetvelde obtained funding from IWT.	We wish to thank the technical support of Ilse Coene en Brecht Crombez.
HCSC	Was supported by a grant RD12/0036/0006 and 15/00059 from ISCIII (Spain), partially supported by European Regional Development FEDER funds	We acknowledge Alicia Tosar and Paula Diaque for their technical assistance
HEBCS	The HEBCS was financially supported by the Helsinki University Hospital Research Fund, Academy of Finland (266528), the Finnish Cancer Society and the Sigrid Juselius Foundation.	HEBCS would like to thank Taru A. Muranen and Johanna Kiiski, Drs. Carl Blomqvist and Kirsimari Aaltonen and RNs Irja Erkkilä and Virpi Palola for their help with the HEBCS data and samples.
HEBON	The HEBON study is supported by the Dutch Cancer Society grants NKI1998-1854, NKI2004-3088, NKI2007-3756, the Netherlands Organisation of Scientific Research grant NWO 91109024, the Pink Ribbon grants 110005 and 2014-187.WO76, the BBMRI grant NWO 184.021.007/CP46 and the Transcan grant JTC 2012 Cancer 12-054.	The Hereditary Breast and Ovarian Cancer Research Group Netherlands (HEBON) consists of the following Collaborating Centers: Netherlands Cancer Institute (coordinating center), Amsterdam, NL: M.A. Rookus, F.B.L. Hogervorst, F.E. van Leeuwen, M.A. Adank, M.K. Schmidt, N.S. Russell, J.L. de Lange, R. Wijnands, D.J. Jenner; Erasmus Medical Center, Rotterdam, NL: J.M. Collée, A.M.W. van den Ouweland, M.J. Hooning, C. Seynaeve, C.H.M. van Deurzen, I.M. Obdeijn; Leiden University Medical Center, NL: C.J. van Asperen, J.T. Wijnen, R.A.E.M. Tollenaar, P. Devilee, T.C.T.E.F. van Cronenburg; Radboud University Nijmegen Medical Center, NL: C.M. Kets, A.R. Mensenkamp; University Medical Center Utrecht, NL: M.G.E.M. Ausems, R.B. van der Luijt, C.C. van der Pol; Amsterdam Medical Center, NL: C.M. Aalfs, H.E.J. Meijers-Heijboer, T.A.M. van Os; VU University Medical Center, Amsterdam, NL: K. van Engelen, J.J.P. Gille, Q. Waisfisz; Maastricht University Medical Center, NL: E.B. Gómez-Garcia, M.J. Blok; University of Groningen, NL: J.C. Oosterwijk, A.H. van der Hout, M.J. Mourits, G.H. de Bock; The Netherlands Comprehensive Cancer Organisation (IKNL): S. Siesling, J.Verloop; The nationwide network and registry of histo- and cytopathology in The Netherlands (PALGA): L.I.H. Overbeek. HEBON thanks the study participants and the registration teams of IKNL and PALGA for part of the data collection.
HRBCP	HRBCP is supported by The Hong Kong Hereditary Breast Cancer Family Registry and the Dr. Ellen Li Charitable Foundation, Hong Kong	We wish to thank Hong Kong Sanatorium and Hospital for their continued support
HUNBOCS	Hungarian Breast and Ovarian Cancer Study was supported by Hungarian Research Grants KTIA-OTKA CK-80745, NKFIH/ OTKA K-112228 and the Norwegian EEA Financial Mechanism Hu0115/NA/2008-3/OP-9	We wish to thank the Hungarian Breast and Ovarian Cancer Study Group members (Janos Papp, Tibor Vaszko, Aniko Bozsik, Timea Pocza, Zoltan Matrai, Gabriella Ivady, Judit Franko, Maria Balogh, Gabriella Domokos, Judit Ferenczi, Department of Molecular Genetics, National Institute of Oncology, Budapest, Hungary) and the clinicians and patients for their contributions to this study.
HVH		We wish to thank the Oncogenetics Group (VHIO) and the High Risk and Cancer Prevention Unit of the University Hospital Vall d'Hebron. Acknowledgements to the Cellex Foundation for providing research facilities and equipment.
ICO	The authors would like to particularly acknowledge the support of the Asociación Española Contra el Cáncer (AECC), the Instituto de Salud Carlos III (organismo adscrito al Ministerio de Economía y Competitividad) and "Fondo Europeo de Desarrollo Regional (FEDER), una manera de hacer Europa" (PI10/01422, PI13/00285, PIE13/00022, PI15/00854, PI16/00563 and CIBERONC) and the Institut Català de la Salut and Autonomous Government of Catalonia (2009SGR290, 2014SGR338 and PERIS Project MedPerCan).ICO: Contract grant sponsor: Asociación Española Contra el Cáncer, Spanish Health Research Fund; Carlos III Health Institute; Catalan Health Institute and Autonomous Government of Catalonia. Contract grant numbers: ISCIIIRETIC RD06/0020/1051, RD12/0036/008, PI10/01422, PI10/00748, PI13/00285, PIE13/00022, 2009SGR290 and 2014SGR364.	We wish to thank the ICO Hereditary Cancer Program team led by Dr. Gabriel Capella.

(Continues)

IHCC	The IHCC was supported by Grant PBZ_KBN_122/P05/2004	
ILUH	The ILUH group was supported by the Icelandic Association "Walking for Breast Cancer Research" and by the Landspitali University Hospital Research Fund.	
INHERIT	This work was supported by the Canadian Institutes of Health Research for the "CIHR Team in Familial Risks of Breast Cancer" program, the Canadian Breast Cancer Research Alliance-grant #019511 and the Ministry of Economic Development, Innovation and Export Trade – grant # PSR-SIIRI-701.	We would like to thank Dr Martine Dumont, Martine Tranchant for sample management and skillful technical assistance. J.S. is Chairholder of the Canada Research Chair in Oncogenetics. J.S. was part of the QC and Genotyping coordinating group of iCOGS (BCAC and CIMBA).
IOVCHBOCS	IOVCHBOCS is supported by Ministero della Salute and "5 × 1000" Istituto Oncologico Veneto grant.	
IPOBCS	This study was in part supported by Liga Portuguesa Contra o Cancro.	We wish to thank Drs. Catarina Santos, Patrícia Rocha and Pedro Pinto for their skillful contribution to the study.
KCONFAB	kConFab is supported by a grant from the National Breast Cancer Foundation, and previously by the National Health and Medical Research Council (NHMRC), the Queensland Cancer Fund, the Cancer Councils of New South Wales, Victoria, Tasmania and South Australia, and the Cancer Foundation of Western Australia; Amanda Spurdle is supported by an NHMRC Senior Research Fellowship.	We wish to thank Heather Thorne, Eveline Niedermayr, all the kConFab research nurses and staff, the heads and staff of the Family Cancer Clinics, and the Clinical Follow Up Study (which has received funding from the NHMRC, the National Breast Cancer Foundation, Cancer Australia, and the National Institute of Health (USA)) for their contributions to this resource, and the many families who contribute to kConFab.
KOHBRA	KOHBRA is partially supported by a grant from the National R&D Program for Cancer Control, Ministry for Health, Welfare and Family Affairs, Republic of Korea (1020350 & 1420190).	
MAYO	MAYO is supported by NIH grants CA116167, CA128978 and CA176785, an NCI Specialized Program of Research Excellence (SPORE) in Breast Cancer (CA116201), a grant from the Breast Cancer Research Foundation, and a generous gift from the David F. and Margaret T. Grohne Family Foundation.	
MCGILL	Jewish General Hospital Weekend to End Breast Cancer, Quebec Ministry of Economic Development, Innovation and Export Trade	
MODSQUAD	MODSQUAD was supported by MH CZ - DRO (MMCI, 00209805) and by the project MEYS-NPS I- LO1413, and by Charles University in Prague project UNCE204024 (MZ).	Modifier Study of Quantitative Effects on Disease (MODSQUAD): MODSQUAD acknowledges ModSQuaD members and Michal Zikan, Petr Pohlreich and Zdenek Kleibl (Oncogynecologic Center and Department of Biochemistry and Experimental Oncology, First Faculty of Medicine, Charles University, Prague, Czech Republic).
MUV		We wish to thank Daniela Muhr and the Senology team, and the clinicians and patients for their contributions to this study.
MSKCC	MSKCC is supported by grants from the Breast Cancer Research Foundation, the Robert and Kate Niehaus Clinical Cancer Genetics Initiative, the Andrew Sabin Research Fund. and the NIH/NCI Cancer Center Support Grant P30 CA008748.	Anne Lincoln, Lauren Jacobs
MUV		We wish to thank Daniela Muhr and the Senology team, and the clinicians and patients for their contributions to this study.
NCCS	Dr J Ngeow is supported by grants from National Medical Research Council of Singapore; Ministry of Health Health Services Research Grant Singapore and Lee Foundation Singapore	We would like to thank all patients, families and clinicians who contributed data and time to this study.
NCI	The research of Drs. MH Greene, PL Mai, and JT Loud was supported by the Intramural Research Program of the US National Cancer Institute, NIH, and by support services contracts NO2-CP-11019-50 and N02-CP-65504 with Westat, Inc, Rockville, MD.	
NNPIO	This work has been supported by the Russian Federation for Basic Research (grants 14-04-93959 and 15-04-01744).	
Northshore		We would like to thank Wendy Rubinstein and the following genetic counselors for help with participant recruitment: Scott Weissman, Anna Newlin, Kristen Vogel, Lisa Dellafave-Castillo, Shelly Weiss.
NRG Oncology	This study was supported by NRG Oncology Operations grant number U10 CA180868 as well as NRG SDMC grant U10 CA180822, Gynecologic Oncology Group (GOG) Administrative Office and the GOG Tissue Bank (CA 27469) and the GOG Statistical and Data Center (CA 37517). Drs. Greene, Mai and Loud were supported by funding from the Intramural Research Program, NCI.	We thank the investigators of the Australia New Zealand NRG Oncology group
OCGN		We wish to thank members and participants in the Ontario Cancer Genetics Network for their contributions to the study.

(Continues)

OSUCCG	OSUCCG is supported by the Ohio State University Comprehensive Cancer Center.	Kevin Sweet, Caroline Craven, Julia Cooper, and Michelle O'Conor were instrumental in accrual of study participants, ascertainment of medical records and database management.
PBCS	This work was supported by the ITT (Istituto Toscano Tumori) grants 2011–2013.	
SEABASS	Ministry of Science, Technology and Innovation, Ministry of Higher Education (UM.C/HIR/MOHE/06) and Cancer Research Initiatives Foundation	We would like to thank Yip Cheng Har, Nur Aishah Mohd Taib, Phuah Sze Yee, Norhashimah Hassan and all the research nurses, research assistants and doctors involved in the MyBrCa Study for assistance in patient recruitment, data collection and sample preparation. In addition, we thank Philip Iau, Sng Jen-Hwei and Sharifah Nor Akmal for contributing samples from the Singapore Breast Cancer Study and the HUKM-HKL Study respectively. The Malaysian Breast Cancer Genetic Study is funded by research grants from the Malaysian Ministry of Science, Technology and Innovation, Ministry of Higher Education (UM.C/HIR/MOHE/06) and charitable funding from Cancer Research Initiatives Foundation.
SMC	This project was partially funded through a grant by the Israel cancer association and the funding for the Israeli Inherited breast cancer consortium	SMC team wishes to acknowledge the assistance of the Meirav Comprehensive breast cancer center team at the Sheba Medical Center for assistance in this study.
SWE-BRCA	SWE-BRCA collaborators are supported by the Swedish Cancer Society	Swedish scientists participating as SWE-BRCA collaborators are: from Lund University and University Hospital: Åke Borg, Håkan Olsson, Helena Jernström, Karin Henriksson, Katja Harbst, Maria Soller, Ulf Kristoffersson; from Gothenburg Sahlgrenska University Hospital: Margareta Nordling, Per Karlsson, Zakaria Einbeigi; from Stockholm and Karolinska University Hospital: Annika Lindblom, Brita Arver, Gisela Barbany Bustinza, Johanna Rantala; from Umeå University Hospital: Beatrice Melin, Christina Edwinsdotter Ardnor, Monica Emanuelsson; from Uppsala University: Maritta Hellström Pigg, Richard Rosenquist; from Linköping University Hospital: Marie Stenmark-Askmalm, Sigrun Liedgren
UCHICAGO	UCHICAGO is supported by NCI Specialized Program of Research Excellence (SPORE) in Breast Cancer (CA125183), R01 CA142996, 1U01CA161032 and by the Ralph and Marion Falk Medical Research Trust, the Entertainment Industry Fund National Women's Cancer Research Alliance and the Breast Cancer research Foundation. OIO is an ACS Clinical Research Professor.	We wish to thank Cecilia Zvocec, Qun Niu, physicians, genetic counselors, research nurses and staff of the Cancer Risk Clinic for their contributions to this resource, and the many families who contribute to our program.
UCLA	Jonsson Comprehensive Cancer Center Foundation; Breast Cancer Research Foundation	We thank Joyce Seldon MSGC and Lorna Kwan, MPH for assembling the data for this study.
UCSF	UCSF Cancer Risk Program and Helen Diller Family Comprehensive Cancer Center	We would like to thank the following genetic counselors for participant recruitment: Beth Crawford, Kate Loranger, Julie Mak, Nicola Stewart, Robin Lee, and Peggy Conrad. And thanks to Ms. Salina Chan for her data management.
UKFOCR	UKFOCR was supported by a project grant from CRUK to Paul Pharoah.	We thank Simon Gayther, Carole Pye, Patricia Harrington and Eva Wozniak for their contributions toward the UKFOCR.
UPENN	National Institutes of Health (NIH) (R01-CA102776 and R01-CA083855; Breast Cancer Research Foundation; Susan G. Komen Foundation for the cure, Basser Research Center for BRCA	
UPITT/MWH	Frieda G. and Saul F. Shapira BRCA-Associated Cancer Research Program; Hackers for Hope Pittsburgh	
VFCTG	Victorian Cancer Agency, Cancer Australia, National Breast Cancer Foundation	Geoffrey Lindeman, Marion Harris, Martin Delatycki of the Victorian Familial Cancer Trials Group. We thank Sarah Sawyer and Rebecca Driessen for assembling this data and Ella Thompson for performing all DNA amplification.
WCP	Beth Y. Karlan was supported by the American Cancer Society Early Detection Professorship (SIOP-06-258-06-COUN) and the National Center for Advancing Translational Sciences (NCATS), Grant UL1TR000124	

REFERENCES

Abugattas, J., Llacuachaqui, M., Allende, Y. S., Velásquez, A. A., Velarde, R., Cotrina, J., … Narod, S. A. (2015). Prevalence of BRCA1 and BRCA2 mutations in unselected breast cancer patients from Peru. *Clinical Genetics*, *88*(4), 371–375.

Ah Mew, N., Hamel, N., Galvez, M., Al-Saffar, M., & Foulkes, W. D. (2002). Haplotype analysis of a BRCA1: 185delAG mutation in a Chilean family supports its Ashkenazi origins. *Clinical Genetics*, *62*(2), 151–156.

Ahn, S. H., Son, B. H., Yoon, K. S., Noh, D. Y., Han, W., Kim, S. W., … Cho, D. Y. (2007). BRCA1 and BRCA2 germline mutations in Korean breast cancer patients at high risk of carrying mutations. *Cancer Letters*, *245*(1-2), 90–95.

Alemar, B., Herzog, J., Brinckmann, O. N. C., Artigalás, O., Schwartz, I. V. D., Matzenbacher Bittar, C., … Weitzel, J. N. (2016). Prevalence of Hispanic BRCA1 and BRCA2 mutations among hereditary breast and ovarian cancer patients from Brazil reveals differences

among Latin American populations. *Cancer Genetics*, *209*(9), 417–422.

Anczukow, O., Ware, M. D., Buisson, M., Zetoune, A. B., Stoppa-Lyonnet, D., Sinilnikova, O. M., & Mazoyer, S. (2008). Does the nonsense-mediated mRNA decay mechanism prevent the synthesis of truncated BRCA1, CHK2, and p53 proteins? *Human Mutation*, *29*(1), 65–73.

Antoniou, A. C., Sinilnikova, O. M., Simard, J., Léoné, M., Dumont, M., Neuhausen, S. L., … Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA) (2007). RAD51 135G→C modifies breast cancer risk among BRCA2 mutation carriers: Results from a combined analysis of 19 studies. *American Journal of Human Genetics*, *81*(6), 1186–1200.

Bergthorsson, J. T., Jonasdottir, A., Johannesdottir, G., Arason, A., Egilsson, V., Gayther, S., … Barkardottir, R. B. (1998). Identification of a novel splice-site mutation of the BRCA1 gene in two breast cancer families: Screening reveals low frequency in Icelandic breast cancer patients. *Human Mutation Suppl*, *1*, S195–7.

Bernstein, J. L., Teraoka, S., Southey, M. C., Jenkins, M. A., Andrulis, I. L., Knight, J. A., … Concannon, P. (2006). Population-based estimates of breast cancer risks associated with ATM gene variants c.7271T>G and c.1066-6T>G (IVS10-6T>G) from the breast cancer family registry. *Human Mutation*, *27*(11), 1122–1128.

Bu, R., Siraj, A. K., Al-Obaisi, K. A., Beg, S., Al Hazmi, M., Ajarim, D., … Al-Kuraya, K. S. (2016). Identification of novel BRCA founder mutations in Middle Eastern breast cancer patients using capture and Sanger sequencing analysis. *International Journal of Cancer*, *139*(5), 1091–1097.

Buisson, M., Anczukow, O., Zetoune, A. B., Ware, M. D., & Mazoyer, S. (2006). The 185delAG mutation (c.68_69delAG) in the BRCA1 gene triggers translation reinitiation at a downstream AUG codon. *Hum Mutat*, *27*(10), 1024–1029.

Chen, S., & Parmigiani, G. (2007). Meta-analysis of BRCA1 and BRCA2 penetrance. *Journal of Clinical Oncology*, *25*(11), 1329–1333.

Chenevix-Trench, G., Milne, R. L., Antoniou, A. C., Couch, F. J., Easton, D. F., & Goldgar, D. E. (2007). An international initiative to identify genetic modifiers of cancer risk in BRCA1 and BRCA2 mutation carriers: The consortium of investigators of modifiers of BRCA1 and BRCA2 (CIMBA). *Breast Cancer Research*, *9*(2), 104.

Cock-Rada, A. M., Ossa, C. A., Garcia, H. I., & Gomez, L. R. 2017. A multigene panel study in hereditary breast and ovarian cancer in Colombia. *Familial Cancer*, *17*(1), 23–30

Domchek, S. M., Friebel, T. M., Singer, C. F., Evans, D. G., Lynch, H. T., Isaacs, C., … Rebbeck, T. R. (2010). Association of Risk-Reducing Surgery in BRCA1 or BRCA2 Mutation Carriers With Cancer Risk and Mortality. *Jama-Journal of the American Medical Association*, *304*(9), 967–975.

Eachkoti, R., Hussain, I., Afroze, D., Aejazaziz, S., Jan, M., Shah, Z. A., … Siddiqi, M. A. (2007). BRCA1 and TP53 mutation spectrum of breast carcinoma in an ethnic population of Kashmir, an emerging high-risk area. *Cancer Letters*, *248*(2), 308–320.

Ferla, R., Calo, V., Cascio, S., Rinaldi, G., Badalamenti, G., Carreca, I., … Russo, A. (2007). Founder mutations in BRCA1 and BRCA2 genes. *Annals of Oncology*, *18*(Suppl 6), vi93–8.

Friedman, E., Bar-Sade Bruchim, R., Kruglikova, A., Risel, S., Levy-Lahad, E., Halle, D., … Abeliovich, A. D. (1998). Double heterozygotes for the Ashkenazi founder mutations in BRCA1 and BRCA2 genes. *American Journal of Human Genetics*, *63*(4), 1224–1227.

Gao, Q., Tomlinson, G., Das, S., Cummings, S., Sveen, L., Fackenthal, J., … Olopade, O. I. (2000). Prevalence of BRCA1 and BRCA2 mutations among clinic-based African American families with breast cancer. *Human Genetics*, *107*(2), 186–191.

Gayther, S. A., Harrington, P., Russell, P., Kharkevich, G., Garkavtseva, R. F., & Ponder, B. A. (1997). Frequently occurring germ-line mutations of the BRCA1 gene in ovarian cancer families from Russia. *American Journal of Human Genetics*, *60*(5), 1239–1242.

Gayther, S. A., Mangion, J., Russell, P., Seal, S., Barfoot, R., Ponder, B. A., … Easton, D. (1997). Variation of risks of breast and ovarian cancer associated with different germline mutations of the BRCA2 gene. *Nature Genetics*, *15*(1), 103–105.

Gayther, S. A., Warren, W., Mazoyer, S., Russell, P. A., Harrington, P. A., Chiano, M., … Dunning, A. M. (1995). Germline mutations of the BRCA1 gene in breast and ovarian cancer families provide evidence for a genotype-phenotype correlation. *Nature Genetics*, *11*(4), 428–433.

Goldgar, D. E., Easton, D. F., Deffenbaugh, A. M., Monteiro, A. N., Tavtigian, S. V., & Couch, F. J. (2004). Integrated evaluation of DNA sequence variants of unknown clinical significance: Application to BRCA1 and BRCA2. *American Journal of Human Genetics*, *75*(4), 535–544.

Gonzalez-Hormazabal, P., Gutierrez-Enriquez, S., Gaete, D., Reyes, J. M., Peralta, O., Waugh, E., … Jara, L. (2011). Spectrum of BRCA1/2 point mutations and genomic rearrangements in high-risk breast/ovarian cancer Chilean families. *Breast Cancer Research and Treatment*, *126*(3), 705–716.

Gorski, B., Byrski, T., Huzarski, T., Jakubowska, A., Menkiszak, J., Gronwald, J., … Lubiński, J. (2000). Founder mutations in the BRCA1 gene in Polish families with breast-ovarian cancer. *American Journal of Human Genetics*, *66*(6), 1963–1968.

Hamel, N., Feng, B. J., Foretova, L., Stoppa-Lyonnet, D., Narod, S. A., Imyanitov, E., … Foulkes, W. D. (2011). On the origin and diffusion of BRCA1 c.5266dupC (5382insC) in European populations. *European Journal of Human Genetics*, *19*(3), 300–306.

Hansen, T. V., Ejlertsen, B., Albrechtsen, A., Bergsten, E., Bjerregaard, P., Hansen, T., … Nielsen, F. C. (2009). A common Greenlandic Inuit BRCA1 RING domain founder mutation. *Breast Cancer Research and Treatment*, *115*(1), 69–76.

Ho, G. H., Phang, B. H., Ng, I. S., Law, H. Y., Soo, K. C., & Ng, E. H. (2000). Novel germline BRCA1 mutations detected in women in singapore who developed breast carcinoma before the age of 36 years. *Cancer*, *89*(4), 811–816.

Jara, L., Ampuero, S., Santibanez, E., Seccia, L., Rodriguez, J., Bustamante, M., … Reyes, J. M. (2006). BRCA1 and BRCA2 mutations in a South American population. *Cancer Genetics and Cytogenetics*, *166*(1), 36–45.

John, E. M., Miron, A., Gong, G., Phipps, A. I., Felberg, A., Li, F. P., … Whittemore, A. S. (2007). Prevalence of pathogenic BRCA1 mutation carriers in 5 US racial/ethnic groups. *Journal of the American Medical Association*, *298*(24), 2869–2876.

Kadalmani, K., Deepa, S., Bagavathi, S., Anishetty, S., Thangaraj, K., & Gajalakshmi, P. (2007). Independent origin of 185delAG BRCA1 mutation in an Indian family. *Neoplasma*, *54*(1), 51–56.

Kaufman, B., Laitman, Y., Gronwald, J., Lubinski, J., & Friedman, E. (2009). Haplotype of the C61G BRCA1 mutation in Polish and Jewish individuals. *Genetic Testing and Molecular Biomarkers*, *13*(4), 465–469.

Kuchenbaecker, K. B., Hopper, J. L., Barnes, D. R., Phillips, K. A., Mooij, T. M., Roos-Blom, M. J., … Olsson, H. (2017). Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers. *Journal of the American Medical Association*, *317*(23), 2402–2416.

Kurian, A. W. (2010). BRCA1 and BRCA2 mutations across race and ethnicity: Distribution and clinical implications. *Current Opinion in Obstetrics Gynecology*, *22*(1), 72–78.

Laitman, Y., Borsthein, R. T., Stoppa-Lyonnet, D., Dagan, E., Castera, L., Goislard, M., … Friedman, E. (2011). Germline mutations in BRCA1 and BRCA2 genes in ethnically diverse high risk families in Israel. *Breast Cancer Research and Treatment*, *127*(2), 489–495.

Laitman, Y., Feng, B. J., Zamir, I. M., Weitzel, J. N., Duncan, P., Port, D., … Friedman, E. (2013). Haplotype analysis of the 185delAG BRCA1 mutation in ethnically diverse populations. *European Journal of Human Genetics*, *21*(2), 212–216.

Lang, G. T., Shi, J. X., Hu, X., Zhang, C. H., Shan, L., Song, C. G., … Shao, Z. M. (2017). The spectrum of BRCA mutations and characteristics of BRCA-associated breast cancers in China: Screening of 2,991 patients and 1,043 controls by next-generation sequencing. *International Journal of Cancer*, *141*(1), 129–142.

Lee, A. S., Ho, G. H., Oh, P. C., Balram, C., Ooi, L. L., Lim, D. T., … Hong, G. S. (2003). Founder mutation in the BRCA1 gene in Malay breast cancer patients from Singapore. *Human Mutation*, *22*(2), 178.

Li, N., Zhang, X., Cai, Y., Xu, X., Zhang, L., Pan, K. F., … Wang, M. R. (2006). BRCA1 germline mutations in Chinese patients with hereditary breast and ovarian cancer. *International Journal of Gynecological Cancer*, *16*(Suppl 1):172–178.

Lord, C. J., & Ashworth, A. (2017). PARP inhibitors: Synthetic lethality in the clinic. *Science*, *355*(6330), 1152–1158.

Maxwell, K. N., Domchek, S. M., Nathanson, K. L., & Robson, M. E. (2016). Population Frequency of Germline BRCA1/2 Mutations. *Journal of Clinical Oncology*, *34*(34), 4183–4185.

Mikaelsdottir, E. K., Valgeirsdottir, S., Eyfjord, J. E., & Rafnar, T. (2004). The Icelandic founder mutation BRCA2 999del5: analysis of expression. *Breast Cancer Res 6*(4), R284–R290.

Moslehi, R., Russo, D., Phelan, C., Jack, E., Antman, K., & Narod, S. (2000). An unaffected individual from a breast/ovarian cancer family with germline mutations in both BRCA1 and BRCA2. *Clinical Genetics*, *57*(1), 70–73.

Nanda, R., Schumm, L. P., Cummings, S., Fackenthal, J. D., Sveen, L., Ademuyiwa, F., … Olopade, O. I. (2005). Genetic testing in an ethnically diverse cohort of high-risk women: A comparative analysis of BRCA1 and BRCA2 mutations in American families of European and African ancestry. *Journal of the American Medical Association*, *294*(15), 1925–1933.

NCCN. (2017). Updates in version 2.2017 of the NCCN guidelines for genetic/familial high-risk assessment: Breast and ovarian cancer.

Neuhausen, S. L., Godwin, A. K., Gershoni-Baruch, R., Schubert, E., Garber, J., Stoppa-Lyonnet, D., … Goldgar, D. (1998). Haplotype and phenotype analysis of nine recurrent BRCA2 mutations in 111 families: Results of an international study. *American Journal of Human Genetics*, *62*(6), 1381–1388.

Neuhausen, S. L., Mazoyer, S., Friedman, L., Stratton, M., Offit, K., Caligo, A., … Goldgar, D. E. (1996). Haplotype and phenotype analysis of six recurrent BRCA1 mutations in 61 families: Results of an international study. *American Journal of Human Genetics*, *58*(2), 271–280.

Oros, K. K., Ghadirian, P., Maugard, C. M., Perret, C., Paredes, Y., Mes-Masson, A. M., … Tonin, P. N. (2006a). Application of BRCA1 and BRCA2 mutation carrier prediction models in breast and/or ovarian cancer families of French Canadian descent. *Clinical Genetics*, *70*(4), 320–329.

Oros, K. K., Leblanc, G., Arcand, S. L., Shen, Z., Perret, C., Mes-Masson, A. M., … Tonin, P. N. (2006b). Haplotype analysis suggest common founders in carriers of the recurrent BRCA2 mutation, 3398delAAAAG, in French Canadian hereditary breast and/ovarian cancer families. *BMC Medical Genetics*, *7*, 23.

Ossa, C. A., & Torres, D. (2016). Founder and Recurrent Mutations in BRCA1 and BRCA2 Genes in Latin American Countries: State of the Art and Literature Review. *Oncologist*, *21*(7), 832–839.

Ostrander, E. A., & Udler, M. S. (2008). The role of the BRCA2 gene in susceptibility to prostate cancer revisited. *Cancer Epidemiology Biomarkers & Prevention*, *17*(8), 1843–1848.

Pal, T., Permuth-Wey, J., Holtje, T., & Sutphen, R. (2004). BRCA1 and BRCA2 mutations in a study of African American breast cancer patients. *Cancer Epidemiology, Biomarkers & Prevention*, *13*(11 Pt 1), 1794–1799.

Palomba, G., Cossu, A., Friedman, E., Budroni, M., Farris, A., Contu, A., … Palmieri, G. (2007). Origin and distribution of the BRCA2-8765delAG mutation in breast cancer. *BMC Cancer*, *7*(1), 132.

Perrin-Vidoz, L., Sinilnikova, O. M., Stoppa-Lyonnet, D., Lenoir, G. M., & Mazoyer, S. (2002). The nonsense-mediated mRNA decay pathway triggers degradation of most BRCA1 mRNAs bearing premature termination codons. *Human Molecular Genetics*, *11*(23), 2805–2814.

Peto, J., Collins, N., Barfoot, R., Seal, S., Warren, W., Rahman, N., … Stratton, M. R. (1999). Prevalence of BRCA1 and BRCA2 gene mutations in patients with early-onset breast cancer. *Journal of National Cancer Institute*, *91*(11), 943–949.

Pisano, M., Cossu, A., Persico, I., Palmieri, G., Angius, A., Casu, G., … Tanda, F. (2000). Identification of a founder BRCA2 mutation in Sardinia. *British Journal of Cancer*, *82*(3), 553–559.

Pritchard, C. C., Mateo, J., Walsh, M. F., De Sarkar, N., Abida, W., Beltran, H., … Nelson, P. S. (2016). Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer. *The New England Journal of Medicine*, *375*(5), 443–453.

Ramus, S. J., Friedman, L. S., Gayther, S. A., Ponder, B. A., Bobrow, L., van der Looji, M., … Olah, E. (1997a). A breast/ovarian cancer patient with germline mutations in both BRCA1 and BRCA2. *Nature Genetics*, *15*(1), 14–15.

Ramus, S. J., Kote-Jarai, Z., Friedman, L. S., van der Looij, M., Gayther, S. A., Csokay, B., … Olah, E. (1997b). Analysis of BRCA1 and BRCA2 mutations in Hungarian families with breast or breast-ovarian cancer. *American Journal of Human Genetics*, *60*(5), 1242–1246.

Rashid, M. U., Zaidi, A., Torres, D., Sultan, F., Benner, A., Naqvi, B., … Hamann, U. (2006). Prevalence of BRCA1 and BRCA2 mutations in Pakistani breast and ovarian cancer patients. *International Journal of Cancer*, *119*(12), 2832–2839.

Rebbeck, T. R., Friebel, T. M., Mitra, N., Wan, F., Chen, S., Andrulis, I. L., … Ramus, S. J. (2016). Inheritance of deleterious mutations at both BRCA1 and BRCA2 in an international sample of 32,295 women. *Breast Cancer Research*, *18*(1), 112.

Rebbeck, T. R., Lynch, H. T., Neuhausen, S. L., Narod, S. A., Van't Veer, L., Garber, J. E., … Prevention and Observation of Surgical End Points Study Group (2002). Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations. *The New England Journal of Medicine*, *346*(21), 1616–1622.

Rebbeck, T. R., Mitra, N., Wan, F., Sinilnikova, O. M., Healey, S., McGuffog, L., … Andrulis, I. (2015). Association of type and location of BRCA1 and BRCA2 mutations with risk of breast and ovarian cancer. *Journal of the American Medical Association*, *313*(13), 1347–1361.

Reeves, M. D., Yawitch, T. M., van der Merwe, N. C., van den Berg, H. J., Dreyer, G., & van Rensburg, E. J. (2004). BRCA1 mutations in South African breast and/or ovarian cancer families: Evidence of a novel founder mutation in Afrikaner families. *International Journal of Cancer*, *110*(5), 677–682.

Roa, B. B., Boyd, A. A., Volcik, K., & Richards, C. S. (1996). Ashkenazi Jewish population frequencies for common mutations in BRCA1 and BRCA2. *Nature Genetics*, *14*(2), 185–187.

Rodríguez, A. O., Llacuachaqui, M., Pardo, G. G., Royer, R., Larson, G., Weitzel, J. N., & Narod, S. A. (2012). BRCA1 and BRCA2 mutations among ovarian cancer patients from Colombia. *Gynecologic Oncology*, *124*(2), 236–243.

Saslow, D., Boetes, C., Burke, W., Harms, S., Leach, M. O., Lehman, C. D., … American Cancer Society Breast CancerAdvisory Group (2007). American Cancer Society guidelines for breast screening with MRI as an

adjunct to mammography. *CA: A Cancer Journal for Clinicians*, *57*(2), 75–89.

Seong, M. W., Cho, S., Noh, D. Y., Han, W., Kim, S. W., Park, C. M., … Park, S. S. (2009). Comprehensive mutational analysis of BRCA1/BRCA2 for Korean breast cancer patients: Evidence of a founder mutation. *Clinical Genetics*, *76*(2), 152–160.

Sharifah, N. A., Nurismah, M. I., Lee, H. C., Aisyah, A. N., Clarence-Ko, C. H., Naqiyah, I., … Nor Hisham, A. (2010). Identification of novel large genomic rearrangements at the BRCA1 locus in Malaysian women with breast cancer. *Cancer Epidemiology*, *34*(4), 442–447.

Solano, A. R., Cardoso, F. C., Romano, V., Perazzo, F., Bas, C., Recondo, G., … Mando, O. G. (2017). Spectrum of BRCA1/2 variants in 940 patients from Argentina including novel, deleterious and recurrent germline mutations: Impact on healthcare and clinical practice. *Oncotarget*, *8*(36), 60487–60495.

Song, C. G., Hu, Z., Yuan, W. T., Di, G. H., Shen, Z. Z., Huang, W., & Shao, Z. M. (2005). [Mutational analysis of BRCA1 and BRCA2 genes in early-onset breast cancer patients in Shanghai]. *Zhonghua Yi Xue Za Zhi*, *85*(43), 3030–3034.

Song, C. G., Hu, Z., Yuan, W. T., Di, G. H., Shen, Z. Z., Huang, W., & Shao, Z. M. (2006). [BRCA1 and BRCA2 gene mutations of familial breast cancer from Shanghai in China]. *Zhonghua Yi Xue Yi Chuan Xue Za Zhi*, *23*(1), 27–31.

Struewing, J. P., Hartge, P., Wacholder, S., Baker, S. M., Berlin, M., McAdams, M., … Tucker, M. A. (1997). The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. *The New England Journal of Medicine*, *336*(20), 1401–1408.

Thompson, E. R., Rowley, S. M., Li, N., McInerny, S., Devereux, L., Wong-Brown, M. W., … Campbell, I. G. (2016). Panel Testing for Familial Breast Cancer: Calibrating the Tension Between Research and Clinical Care. *Journal of Clinical Oncology*, *34*(13), 1455–1459.

Thorlacius, S., Olafsdottir, G., Tryggvadottir, L., Neuhausen, S., Jonasson, J. G., Tavtigian, S. V., … Eyfjord, J. E. (1996). A single BRCA2 mutation in male and female breast cancer families from Iceland with varied cancer phenotypes. *Nature Genetics*, *13*(1), 117–119.

Toh, G. T., Kang, P., Lee, S. S., Lee, D. S., Lee, S. Y., Selamat, S., … Teo, S. H. (2008). BRCA1 and BRCA2 germline mutations in Malaysian women with early-onset breast cancer without a family history. *Public Library of Science ONE*, *3*(4), e2024.

Tonin, P. M., Mes-Masson, A. M., Narod, S. A., Ghadirian, P., & Provencher, D. (1999). Founder BRCA1 and BRCA2 mutations in French Canadian ovarian cancer cases unselected for family history. *Clinical Genetics*, *55*(5), 318–324.

Tonin, P. N., Perret, C., Lambert, J. A., Paradis, A. J., Kantemiroff, T., Benoit, M. H., … Ghadirian, P. (2001). Founder BRCA1 and BRCA2 mutations in early-onset French Canadian breast cancer cases unselected for family history. *International Journal of Cancer*, *95*(3), 189–193.

Torres, D., Rashid, M. U., Gil, F., Umana, A., Ramelli, G., Robledo, J. F., … Hamann, U. (2007). High proportion of BRCA1/2 founder mutations in Hispanic breast/ovarian cancer families from Colombia. *Breast Cancer Research and Treatment*, *103*(2), 225–232.

Troudi, W., Uhrhammer, N., Sibille, C., Dahan, C., Mahfoudh, W., Bouchlaka Souissi, C., … Ben Ammar Elgaaied, A. (2007). Contribution of the BRCA1 and BRCA2 mutations to breast cancer in Tunisia. *Journal of Human Genetics*, *52*(11), 915–920.

van Der Looij, M., Wysocka, B., Brozek, I., Jassem, J., Limon, J., & Olah, E. (2000). Founder BRCA1 mutations and two novel germline BRCA2 mutations in breast and/or ovarian cancer families from North-Eastern Poland. *Human Mutation 15*(5), 480–481.

Velez, C., Palamara, P. F., Guevara-Aguirre, J., Hao, L., Karafet, T., Guevara-Aguirre, M., … Ostrer, H. (2012). The impact of Converso Jews on the genomes of modern Latin Americans. *Human Genetics*, *131*(2), 251–263.

Villarreal-Garza, C., Alvarez-Gómez, R. M., Pérez-Plasencia, C., Herrera, L. A., Herzog, J., Castillo, D., … Weitzel, J. N. (2015a). Significant clinical impact of recurrent BRCA1 and BRCA2 mutations in Mexico. *Cancer*, *121*(3), 372–378.

Villarreal-Garza, C., Weitzel, J. N., Llacuachaqui, M., Sifuentes, E., Magallanes-Hoyos, M. C., Gallardo, L., … Narod, S. A. (2015b). The prevalence of BRCA1 and BRCA2 mutations among young Mexican women with triple-negative breast cancer. *Breast Cancer Reserach and Treatment*, *150*(2), 389–394.

Vogel, K. J., Atchley, D. P., Erlichman, J., Broglio, K. R., Ready, K. J., Valero, V., … Arun, B. (2007). BRCA1 and BRCA2 genetic testing in Hispanic patients: Mutation prevalence and evaluation of the BRCAPRO risk assessment model. *Journal of Clinical Oncology*, *25*(29), 4635–4641.

Ware, M. D., DeSilva, D., Sinilnikova, O. M., Stoppa-Lyonnet, D., Tavtigian, S. V. & Mazoyer, S. (2006). Does nonsense-mediated mRNA decay explain the ovarian cancer cluster region of the BRCA2 gene? *Oncogene*, *25*(2), 323–328.

Weitzel, J. N., Clague, J., Martir-Negron, A., Ogaz, R., Herzog, J., Ricker, C., … Larson, G. P. (2013). Prevalence and type of BRCA mutations in Hispanics undergoing genetic cancer risk assessment in the southwestern United States: A report from the Clinical Cancer Genetics Community Research Network. *Journal of Clinical Oncology*, *31*(2), 210–216.

Weitzel, J. N., Lagos, V., Blazer, K. R., Nelson, R., Ricker, C., Herzog, J., … Neuhausen, S. (2005). Prevalence of BRCA mutations and founder effect in high-risk Hispanic families. *Cancer Epidemiology, Biomarkers & Prevention*, *14*(7), 1666–1671.

Weitzel, J. N., Lagos, V. I., Herzog, J. S., Judkins, T., Hendrickson, B., Ho, J. S., … Scholl, T. (2007). Evidence for common ancestral origin of a recurring BRCA1 genomic rearrangement identified in high-risk hispanic families. *Cancer Epidemiology, Biomarkers & Prevention*, *16*(8), 1615–1620.

Welcsh, P. L., & King, M. C. (2001). BRCA1 and BRCA2 and the genetics of breast and ovarian cancer. *Human Molecular Genetics*, *10*(7), 705–713.

Whittemore, A. S., Gong, G., John, E. M., McGuire, V., Li, F. P., Ostrow, K. L., … West, D. W. (2004). Prevalence of BRCA1 mutation carriers among U.S. non-Hispanic Whites. *Cancer Epidemiology, Biomarkers & Prevention*, *13*(12), 2078–2083.

Zhang, B., Fackenthal, J. D., Niu, Q., Huo, D., Sveen, W. E., DeMarco, T., … Olopade, O. I. (2009). Evidence for an ancient BRCA1 mutation in breast cancer patients of Yoruban ancestry. *Familial Cancer*, *8*(1), 15–22.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Rebbeck TR, Friebel TM, Friedman E, et al. Mutational spectrum in a worldwide study of 29,700 families with *BRCA1* or *BRCA2* mutations. *Human Mutation*. 2018;39:593–620. https://doi.org/10.1002/humu.23406