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 MBBS[11], Fergus J. Couch[12], David E. Goldgar[13], Torben A. Kruse[9], Edenir Inêz Palmero[14], Sue Kyung Park[15], Diana Torres[3,16], Elizabeth J. van Rensburg[17], Lesley McGuffog[18], Michael T. Parsons[19], Goska Leslie MEng[18], Cora M. Aalfs[20], Julio Abugattas[21], Julian Adlard[22], Simona Agata[23], Kristiina Aittomäki[24], Lesley Andrews[25], Irene L. Andrulis[26], Adalgeir Arason[27], Norbert Arnold[28], Banu K. Arun[29], Ella Asseryanis[30], Leo Auerbach[30], Jacopo Azzollini[31], Judith Balmaña[32], Monica Barile[33], Rosa B. Barkardottir[34], Daniel Barrowdale[18], Javier Benitez[35], Andreas Berger[36], Raanan Berger[37], Amie M. Blanco[38], Kathleen R. Blazer[10], Marinus J. Blok[39], Valérie Bonadona[40], Bernardo Bonanni[33], Angela R. Bradbury[41], Carole Brewer[42], Bruno Buecher[43], Saundra S. Buys[44], Trinidad Caldes[45], Almuth Caliebe[46], Maria A. Caligo[47], Ian Campbell[48], Sandrine Caputo[43], Jocelyne Chiquette[49], Wendy K. Chung[50], Kathleen B.M. Claes[51], J. Margriet Collée[52], Jackie Cook[53], Rosemarie Davidson[54], Miguel de la Hoya[45], Kim De Leeneer[51], Antoine de Pauw[43], Capucine Delnatte[55], Orland Diez[56], Yuan Chun Ding[57], Nina Ditsch[58], Susan M. Domchek[41], Cecilia M. Dorfling MSc[17], Carolina Velazquez[59], Bernd Dworniczak[60], Jacqueline Eason[61], Douglas F. Easton[18], Ros Eeles[62], Hans Ehrencrona[63], Bent Ejlertsen[64], EMBRACE[18], Christoph Engel[65], Stefanie Engert[66], D. Gareth Evans[67], Laurence Faivre[68], Lidia Feliubadaló[69], Sandra Fert Ferrer[70], Lenka Foretova[71], Jeffrey Fowler[72], Debra Frost[18], Henrique C. R. Galvão[73], Patricia A. Ganz[74], Judy Garber[75], Marion Gauthier-Villars[43], Andrea Gehrig[76], GEMO Study Collaborators[77], Anne-Marie Gerdes[78], Paul Gesta [79], Giuseppe Giannini[80], Sophie Giraud[81], Gord Glendon[82], Andrew K. Godwin[83], Mark H. Greene[84], Jacek Gronwald[85], Angelica Gutierrez-Barrera[29], Eric Hahnen[86], Jan Hauke[86], HEBON[87], Alex Henderson[88], Julia Hentschel[89], Frans B.L. Hogervorst[90], Ellen Honisch[91], Evgeny N. Imyanitov[92], Claudine Isaacs[93], Louise Izatt[94], Angel Izquierdo[95], Anna Jakubowska[85], Paul James[96], Ramunas Janavicius[97], Uffe Birk Jensen[98], Esther M. John[99], Vijai Joseph[100], Katarzyna Kaczmarek[85], Beth Y. Karlan[101], Karin Kast[102], KConFab Investigators[103], Sung-Won Kim[104], Irene Konstantopoulou[105], Jacob Korach[106], Yael Laitman[2], Adriana Lasa[107], Christine Lasset[40], Conxi Lázaro[69], Annette Lee[108], Min Hyuk Lee[109], Jenny Lester MPH[101], Fabienne Lesueur[110], Annelie Liljegren[111], Noralane M. Lindor[112], Michel Longy[113], Jennifer T. Loud[114], Karen H. Lu[115], Jan Lubinski[85], Eva Machackova[71], Siranoush Manoukian[31], Véronique Mari[116], Cristina Martínez-Bouzas[117], Zoltan Matrai[118], Noura Mebirouk[110], Hanne E.J. Meijers-Heijboer[119], Alfons Meindl[66], Arjen R. Mensenkamp[120], Ugnius Mickys[121], Austin Miller[122], Marco Montagna[23], Kirsten B. Moysich[123], Anna Marie Mulligan[124], Jacob Musinsky[100], Susan L. Neuhausen[57], Heli

Nevanlinna[125], Joanne Ngeow[126], Huu Phuc Nguyen[127], Dieter Niederacher[91], Henriette Roed Nielsen[9], Finn Cilius Nielsen[128], Robert L. Nussbaum[129], Kenneth Offit[130], Anna Öfverholm[131], Kai-ren Ong[132], Ana Osorio PhD[133], Laura Papi[134], Janos Papp[6], Barbara Pasini[135], Inge Sokilde Pedersen[136], Ana Peixoto MSc[137], Nina Peruga MSc[85], Paolo Peterlongo[138], Esther Pohl[86], Nisha Pradhan BA[100], Karolina Prajzendanc[85], Fabienne Prieur[139], Pascal Pujol[140], Paolo Radice[141], Susan J. Ramus[142,143], Johanna Rantala[144], Muhammad Usman Rashid[3, 145], , Kerstin Rhiem[86], Mark Robson[146], Gustavo C. Rodriguez[147], Mark T. Rogers[148], Vilius Rudaitis[149], Ane Y. Schmidt[128], Rita Katharina Schmutzler[86], Leigha Senter MS[150], Payal D. Shah[41], Priyanka Sharma[151], Lucy E. Side[152], Jacques Simard[153], Christian F. Singer[30], Anne-Bine Skytte[98], Thomas P. Slavin[10], Katie Snape[154], Hagay Sobol[155], Melissa Southey[155], Linda Steele[57], Doris Steinemann[157], Grzegorz Sukiennicki[85], Christian Sutter[158], Csilla I. Szabo[159], Yen Y. Tan[36], Manuel R. Teixeira[137], Mary Beth Terry[160], Alex Teulé[161], Abigail Thomas MPH[162], Darcy L. Thull MS[163], Marc Tischkowitz[164], Silvia Tognazzo[23], Amanda Ewart Toland[165], Sabine Topka[100], Alison H Trainer[166], Nadine Tung[167], Christi J. van Asperen[168], Annemieke H. van der Hout[169], Lizet E. van der Kolk[170], Rob B. van der Luijt[171], Mattias Van Heetvelde[51], Liliana Varesco[172], Raymonda Varon-Mateeva[173], Ana Vega[174], Cynthia Villarreal-Garza[175], Anna von Wachenfeldt[176], Lisa Walker[177], Shan Wang-Gohrke[178], Barbara Wappenschmidt[85], Bernhard H. F. Weber[179], Drakoulis Yannoukakos[105], Sook-Yee Yoon[8], Cristina Zanzottera[31], Jamal Zidan[180], Kristin K. Zorn[181], Christina G. Hutten Selkirk[182], Peter J. Hulick[183], Georgia Chenevix-Trench[19], Amanda B. Spurdle[19], Antonis C. Antoniou[18], Katherine L. Nathanson[41] for the CIMBA Consortium

[1]Harvard TH Chan School of Public Health and Dana Farber Cancer Institute, 1101 Dana Building, 450 Brookline Ave, Boston, MA 02215, 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), Im Neuenheimer Feld 580, 69120 Heidelberg, Germany

[4]5841 South Maryland Avenue, MC 2115 Chicago, IL, USA

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

[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, Paraguay 2155, C1121ABG, Argentina

[8]Cancer Research Initiatives Foundation, Sime Darby Medical Centre, 1 Jalan SS12/1A, Subang Jaya, 47500, Malaysia

[9]Department of Clinical Genetics, Odense University Hospital, Sonder Boulevard 29, Odense C, Denmark

[10]Clinical Cancer Genetics, City of Hope, 1500 East Duarte Road, Duarte, California 91010 USA

[11]Division of Molecular Pathology, Department of Pathology, Hong Kong Sanatorium & Hospital,1/F Li Shu Fan Block, 2 Village Road, Happy Valley, Hong Kong

[12]Department of Laboratory Medicine and Pathology, and Health Sciences Research, Mayo Clinic, 200 First Street SW, Rochester, Minnesota, USA

[13]Department of Dermatology, University of Utah School of Medicine, 30 North 1900 East, SOM 4B454, Salt Lake City, UT 84132, USA

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

[15]1) Department of Preventive Medicine, Seoul National University College of Medicine; 2) Department of Biomedical Science, Seoul National University Graduate School; 3) Cancer Research Center, Seoul National University, 103 Daehak-ro, Jongno-gu, Seoul, Korea

[16]Institute of Human Genetics, Pontificia Universidad Javeriana, Carrera 7, Bogota, 11001000, Colombia

[17] Cancer Genetics Laboratory, Department of Genetics, University of Pretoria, Private Bag X323, Arcadia 0007, South Africa

[18]Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, University of Cambridge, Strangeways Research Laboratory, Worts Causeway, Cambridge, UK

[19]Genetics and Computational Biology Department, QIMR Berghofer Medical Research Institute, Herston Road, Brisbane, QLD 4006, Australia

[20]Department of Clinical Genetics, Academic Medical Center, P.O. Box 22700, 1100 DE Amsterdam, The Netherlands

[21]City of Hope Clinical Cancer Genomics Community Research Network, 1500 East Duarte Road, Duarte, CA 91010, USA

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

[23]Immunology and Molecular Oncology Unit, Veneto Institute of Oncology IOV - IRCCS, Via Gattamelata 64, Padua, Italy

[24]Department of Clinical Genetics, Helsinki University Hospital, P.O. BOX 160 (Meilahdentie 2), 00029 HUS, Finland

[25]Hereditary Cancer Clinic, Prince of Wales Hospital, High Street, Randwick, NSW 2031 Australia

[26]Lunenfeld-Tanenbaum Research Institute, Sinai Health System, Toronto, Ontario M5G 1X5, Canada; Department of Molecular Genetics, University of Toronto, Toronto, Ontario

[27]Department of Pathology, hus 9, Landspitali-LSH v/Hringbraut, 101 Reykjavik, Iceland

[28]Department of Gynaecology and Obstetrics, University Hospital of Schleswig-Holstein, Campus Kiel, Christian-Albrechts University Kiel, Germany

[29] Department of Breast Medical Oncology and Clinical Cancer Genetics Program, University Of Texas MD Anderson Cancer Center, 1515 Pressler Street, CBP 5, Houston, TX, USA

[30]Dept of OB/GYN and Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria, Waehringer Guertel 18-20, A 1090 Vienna, Austria

[31]Unit of Medical Genetics, Department of Medical Oncology and Hematology, Fondazione IRCCS (Istituto Di Ricovero e Cura a Carattere Scientifico) Instituto Nazionale Tumori (INT), Via Giacomo Venezian 1, 20133 Milan, Italy

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

[33]Division of Cancer Prevention and Genetics, Istituto Europeo di Oncologia (IEO), via Ripamonti 435, 20141 Milan, Italy

[34]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, Vatnsmyrarvegi 16, 101 Reykjavik, Iceland

[35]Human Genetics Group and Genotyping Unit (CEGEN), Human Cancer Genetics Programme, Spanish National Cancer Research Centre (CNIO), Madrid, Spain. Biomedical Network on Rare Diseases (CIBERER), Madrid, Spain

[36]Dept of OB/GYN, Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria, Waehringer Guertel 18-20, 1090 Vienna, Austria

[37]The Institute of Oncology, Chaim Sheba Medical Center, Ramat Gan 52621, Israel

[38]UCSF Cancer Genetics and Prevention Program, San Francisco, CA 94143-1714

[39]Department of Clinical Genetics, Maastricht University Medical Center, P.O. Box 5800, 6202 AZ Maastricht, The Netherlands

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

[41]Department of Medicine, Abramson Cancer Center, Perelman School of Medicine at the University of Pennsylvania, 3400 Civic Center Boulevard, Philadelphia, PA 19104, USA

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

[43]Service de Génétique, Institut Curie, 26, rue d'Ulm, Paris Cedex 05, France

[44]Department of Medicine, Huntsman Cancer Institute, 2000 Circle of Hope, Salt Lake City,

UT 84112, USA

[45]Molecular Oncology Laboratory, Hospital Clinico San Carlos, IdISSC, CIBERONC. Martin Lagos s/n, Madrid, Spain

[46] Institute of Human Genetics, University Hospital of Schleswig-Holstein, Campus Kiel, Christian-Albrechts University Kiel, Germany

[47]Section of Genetic Oncology, Dept. of Laboratory Medicine, University and University Hospital of Pisa, Pisa, Italy

[48]Research Division, Peter MacCallum Cancer Centre, 305 Gratten Street, Melbourne, VIC 3000, Australia

[49]CRCHU de Quebec-oncologie, Centre des maladies du sein Deschênes-Fabia, Hôpital du Saint-Sacrement,1050, chemin Sainte-Foy, Québec Canada

[50]Departments of Pediatrics and Medicine, 1150 St. Nicholas Avenue, Columbia University, New York, NY, 10032 USA

[51]Center for Medical Genetics, Ghent University, De Pintelaan 185, 9000 Gent, Belgium

[52]Department of Clinical Genetics, Family Cancer Clinic, Erasmus University Medical Center, P.O. Box 2040, 3000 CA Rotterdam, The Netherlands

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

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

[55]Unité d'oncogénétique, ICO-Centre René Gauducheau, Boulevard Jacques Monod, 44805 Nantes Saint Herblain Cedex, France

[56]Oncogenetics Group, Vall d'Hebron Institute of Oncology (VHIO), Clinical and Molecular Genetics Area, Vall d'Hebron University Hospital, Passeig Vall d'Hebron 119-129, Barcelona, Spain

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

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

[59]Cáncer Hereditario, Instituto de Biología y Genética Molecular, IBGM, Universidad de Valladolid, Centro Superior de Investigaciones Científicas, UVA-CSIC. Valladolid, Spain

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

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

[62]Oncogenetics Team, The Institute of Cancer Research and Royal Marsden NHS

Foundation Trust, Sutton, UK

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

[64]Department of Oncology, Rigshospitalet, Copenhagen University Hospital, Blegdamsvej 9, DK-2100 Copenhagen, Denmark

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

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

[67]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

[68]Centre de Lutte Contre le Cancer Georges François Leclerc, 1 rue Professeur Marion, BP 77 980, Dijon Cedex, France and Genomic and Immunotherapy Medical Institute, Dijon University Hospital, Dijon, France

[69]Molecular Diagnostic Unit, Hereditary Cancer Program, ICO-IDIBELL (Catalan Institute of Oncology-Bellvitge Biomedical Research Institute), CIBERONC, Gran Via de l'Hospitalet, 199-203. 08908 L'Hospitalet. Barcelona, Spain

[70]Laboratoire de Génétique Chromosomique, Hôtel Dieu Centre Hospitalier, BP 1125 Chambéry, France

[71]Department of Cancer Epidemiology and Genetics, Masaryk Memorial Cancer Institute, Zluty kopec 7, Brno, 65653, Czech Republic

[72]Ohio State University /Columbus Cancer Council, Columbus, OH 43221, USA

[73]Oncogenetics Department, Barretos Cancer Hospital, Barretos, São Paulo, Brazil

[74]UCLA Schools of Medicine and Public Health, Division of Cancer Prevention & Control Research, Jonsson Comprehensive Cancer Center, 650 Charles Young Drive South, Room A2-125 HS, Los Angeles, CA 90095-6900, USA

[75]Cancer Risk and Prevention Clinic, Dana-Farber Cancer Institute, 450 Brookline Avenue, Boston, MA, USA

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

[77]Institut Curie, Department of Tumour Biology, Paris, France; Institut Curie, INSERM U830, Paris, France

[78]Department of Clinical Genetics, Rigshospitalet 4062, Blegdamsvej 9, København Ø, Denmark

[79]Service Régional Oncogénétique Poitou-Charentes, Centre Hospitalier, 79021 Niort

[80]Department of Molecular Medicine, University La Sapienza, and Istituto Pasteur - Fondazione Cenci-Bolognetti, viale Regina Elena 291, 00161 Rome, Italy

[81]Bâtiment Cheney D, Centre Léon Bérard, 28 rue Laënnec, Lyon, France

[82]Ontario Cancer Genetics Network: Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, Toronto, Ontario M5G 1X5, Canada

[83]Department of Pathology and Laboratory Medicine, 3901 Rainbow Boulevard,4019 Wahl Hall East, MS 3040, University of Kansas Medical Center, Kansas City, Kansas, USA

[84]Clinical Genetics Branch, DCEG, NCI, NIH, 9609 Medical Center Drive, Room 6E-454, Bethesda, MD, USA

[85]Department of Genetics and Pathology, Pomeranian Medical University, Unii Lubelskiej 1, Szczecin, Poland

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

[87]The Hereditary Breast and Ovarian Cancer Research Group Netherlands (HEBON), Coordinating center: Netherlands Cancer Institute, Amsterdam, The Netherlands

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

[89]Institute of Human Genetics, University Leipzig, 04107 Leipzig, Germany

[90]Family Cancer Clinic, Netherlands Cancer Institute, P.O. Box 90203, 1006 BE Amsterdam, The Netherlands

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

[92]N.N. Petrov Institute of Oncology, St.-Petersburg 197758, Russia

[93]Lombardi Comprehensive Cancer Center, Georgetown University, 3800 Reservoir Road NW, Washington, DC, USA

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

[95]Genetic Counseling Unit, Hereditary Cancer Program, IDIBGI (Institut d'Investigació Biomèdica de Girona), Catalan Institute of Oncology, CIBERONC, Av. França s/n. 1707 Girona, Spain

[96]Parkville Familial Cancer Centre, Peter MacCallum Cancer Centre, 305 Gratten Street, Melbourne, VIC 3000, Australia

[97]Vilnius University Hospital Santariskiu Clinics, Hereditary Cancer Competence Center

Hematology, Oncology and Transfusion Medicine Center Room P519 Santariskiu st. 2,

LT-08661 Vilnius, Lithuania

[98]Department of Clinical Genetics, Aarhus University Hospital, Brendstrupgaardsvej 21C, Aarhus N, Denmark

[99]Department of Epidemiology, Cancer Prevention Institute of California, 2201 Walnut Avenue, Suite 300, Fremont, CA 94538, USA and Department of Health Research and Policy (Epidemiology) and Stanford Cancer Institute, Stanford University School of Medicine, Stanford, CA, USA

[100]Clinical Genetics Research Laboratory, Dept. of Medicine, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10044, USA

[101]Women's Cancer Program at the Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, 8700 Beverly Boulevard, Suite 290W, Los Angeles, CA, USA

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

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

[104]Department of Surgery, Daerim St. Mary's Hospital, 657 Siheung-daero, Yeongdeungpo-gu, Seoul, Korea

[105]Molecular Diagnostics Laboratory, INRASTES (Institute of Nuclear and Radiological Sciences and Technology), National Centre for Scientific Research "Demokritos", Patriarchou Gregoriou & Neapoleos str., Aghia Paraskevi Attikis, Athens, Greece

[106]The Gyneco-Oncology Department, Chaim Sheba Medical Center, Ramat Gan 52621, Israel

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

[108]The Feinstein Institute for Medical Research 350 Community Drive Manhasset NY

[109]Department of Surgery, Soonchunhyang University and Seoul Hospital, 59 Daesagwan-Ro, Yongsan-Gu, Seoul, Korea

[110]Institut Curie, PSL Research University, Mines ParisTech, Inserm U900, 26 rue d'Ulm, F-75005 Paris, France

[111] Department of Oncology Radiumhemmet and Institution of Oncology and Patology

Karolinska University Hospital and Karolinska Institutet

[112]Department of Health Sciences Research, Mayo Clinic, 13400 E. Scottsdale Blvd., Scottsdale, AZ, USA

[113]Oncogénétique, Institut Bergonié, 229 cours de l'Argonne, 33076 Bordeaux, France

[114]Clinical Genetics Branch, DCEG, NCI, NIH, 9609 Medical Center Drive, Room 6E-536, Bethesda, MD, USA

[115]Department of Gynecological Oncology and Clinical Cancer Genetics Program, University Of Texas MD Anderson Cancer Center, 1515 Pressler Street, CPB 6, Houston, TX, USA

[116]Centre Antoine Lacassagne, 33 Avenue de Valombrose, Nice, France

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

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

[119]Department of Clinical Genetics, VU University Medical Center, P.O. Box 7057, 1007 MB Amsterdam, The Netherlands

[120]Department of Human Genetics, Radboud University Medical Center, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands

[121]Vilnius university Santariskiu hospital, National Center of Pathology, Baublio st. 5, Vilnius, Lithuania

[122]NRG Oncology, Statistics and Data Management Center, Roswell Park Cancer Institute, Elm St & Carlton St, Buffalo, NY 14263, USA

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

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

[125]Department of Obstetrics and Gynecology, University of Helsinki and Helsinki University Hospital, Biomedicum Helsinki, P.O. BOX 700 (Haartmaninkatu 8), 00029 HUS, Finland

[126]Cancer Genetics Service, Division of Medical Oncology, National Cancer Centre Singapore, 11 Hospital Drive, Singapore 169610

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

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

[129]513 Parnassus Ave., HSE 901E, San Francisco, CA. 94143 - 0794, USA

[130]Clinical Genetics Research Laboratory, Dept. of Medicine, Cancer Biology and Genetics, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10044, USA

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

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

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

[134]Unit of Medical Genetics, Department of Biomedical, Experimental and Clinical Sciences, University of Florence, Viale Morgagni 50, 50134 Florence, Italy

[135]Department of Medical Sciences, University of Turin, Via Santena 19, 10126 Turin, Italy

[136]Section of Molecular Diagnostics, Department of Biochemistry, Aalborg University Hospital, Reberbansgade 15, Aalborg, Denmark

[137]Department of Genetics, Portuguese Oncology Institute of Porto (IPO Porto), Porto, Portugal, and Biomedical Sciences Institute (ICBAS), University of Porto, Porto, Portugal

[138]IFOM, The FIRC (Italian Foundation for Cancer Research) Institute of Molecular Oncology, via Adamello 16, 20139 Milan, Italy.

[139]Service de Génétique Clinique Chromosomique et Moléculaire, Hôpital Nord, CHU Saint Etienne, St Etienne cedex 2, France

[140]Unité d'Oncogénétique, CHU Arnaud de Villeneuve, 34295 Montpellier Cedex 5, France

[141]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), c/o Amaedeolab, via GA Amadeo 42, 20133 Milan, Italy

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

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

[144]Department of Clinical Genetics, Karolinska University Hospital L5:03, Stockholm S-171 76, Sweden

[145]Department of Basic Sciences, Shaukat Khanum Memorial Cancer Hospital and Research Centre (SKMCH & RC) 7A, Block R3, Johar Town, Lahore, Punjab 54000, Pakistan

[146]Clinical Genetics Services, Dept. of Medicine, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY, USA

[147]Division of Gynecologic Oncology, North Shore University Health System, Clinical Professor, University of Chicago, 2650 Ridge Avenue, Suite 1507 Walgreens, Evanston, IL 60201, USA

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

[149]Vilnius University Hospital Santariskiu Clinics, Centre of Woman's Health and pathology, Department of Gynecology, Santariskiu st. 2, Vilnius, Lithuania

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

[151]Department of Hematology and Oncology, University of Kansas Medical Center, Suite 210, 2330 Shawnee Mission Parkway, Westwood, KS, USA

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

[153]Genomics Center, Centre Hospitalier Universitaire de Québec Research Center and Laval University, 2705 Laurier Boulevard, Quebec City (Quebec), Canada

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

[155]Département Oncologie Génétique, Prévention et Dépistage, Institut Paoli-Calmettes, 232 boulevard Sainte-Margueritte, Marseille, France

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

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

[158]Department of Human Genetics, University Hospital Heidelberg, Germany

[159]National Human Genome Research Institute, National Institutes of Health Building 50, Room 5312, 50 South Drive, MSC 004, Bethesda, MD, USA

[160]Department of Epidemiology, Columbia University, New York, NY, USA

[161]Genetic Counseling Unit, Hereditary Cancer Program, IDIBELL (Bellvitge Biomedical Research Institute), Catalan Institute of Oncology, CIBERONC, Gran Via de l'Hospitalet, 199-203. 08908 L'Hospitalet, Barcelona, Spain

[162]Department of Health Sciences Research, Mayo Clinic, 200 First Street SW, Rochester, Minnesota, USA

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

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

[165]Division of Human Genetics, Departments of Internal Medicine and Cancer Biology and Genetics, Comprehensive Cancer Center, The Ohio State University, 460 W. 12th Avenue, Columbus, OH, USA

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

[167]Department of Medical Oncology, Beth Israel Deaconess Medical Center, 330 Brookline Avenue Boston, Massachusetts 02215, USA

[168]Department of Clinical Genetics, Leiden University Medical Center, P.O. Box 9600, 2300 RC Leiden, The Netherlands

[169]Department of Genetics, University Medical Center Groningen, University Groningen, The

Netherlands

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

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

[172]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, largo Rosanna Benzi 10, 16132 Genoa, Italy

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

[174]Fundación Pública Galega Medicina Xenómica, calle Choupana s/n, Edificio de Consultas, Planta menos dos Santiago de Compostal, A Coruña, Spain

[175]Departamento de Investigacion y de Tumores Mamarios del Instituto Nacional de Cancerologia, Mexico City; and Centro de Cancer de Mama del Hospital Zambrano Hellion, Tecnologico de Monterrey, San Pedro Garza Garcia, Nuevo Leon.

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

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

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

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

[180]Institute of Oncology, Rivka Ziv Medical Center, 13000 Zefat, Israel

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

[182]Center for Medical Genetics, NorthShore University HealthSystem,1000 Central St, Suite 620, Evanston, IL, USA

[183]Medical Director, Center for Medical Genetics, North Shore University Health System, Clinical Assistant Professor of Medicine, University of Chicago Pritzker School of Medicine, 1000 Central Street, Suite 620, Evanston, IL 60201, USA

Corresponding Author:

Timothy R. Rebbeck, PhD

1101 Dana, 450 Brookline Avenue

Dana Farber Cancer Institute, Boston, MA 02215

T: 617-632-6128

Email: Timothy_Rebbeck@dfci.harvard.edu

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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 Caucasians 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 6 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.

BACKGROUND

Women who carry germline mutations in either *BRCA1* [OMIM 113705] or *BRCA2* [600185] are at a greatly 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 57-65% and 20-50%, respectively (Chen and Parmigiani, 2007; Kuchenbaecker, et al., 2017). For *BRCA2,* average risk estimates range from 35-57% and 5-23%, respectively (Chen and 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* (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 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 also can influence cancer treatment decisions, principally around the use of platinum agents or poly (ADP-ribose) polymerase (PARP) inhibitors (Lord and Ashworth, 2017) or contralateral risk-reducing mastectomy. Increasing 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

0.1-0.3%, and 0.1-0.7%, 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, et al., 2016). As they do not include large genomic rearrangements, some newer population-based estimates may still under-represent 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, et al., 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), and *BRCA2* c.8537_8538del (8765delAG) (Oros, et al., 2006b; Tonin, et al., 1999; Tonin, et al., 2001); the *BRCA1* mutations c.181T>G, and c.4034delA in Central-Eastern Europe (Gorski, et al., 2000); the *BRCA1* c.548-4185del in Mexico (Villarreal-Garza, et al., 2015b; Weitzel, et al., 2013)(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 and 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.; Ho, et al., 2000; Jara, et al., 2006; John, et al., 2007; Kurian, 2010; Laitman, et al.; Lang, et al., 2017; Lee, et al., 2003; Li, et al., 2006; Nanda, et al., 2005; Ossa and Torres, 2016; Pal, et al., 2004; Rodríguez, et al., 2012; Seong, et al., 2009; Sharifah, et al.; 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).

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/h (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.

RESULTS

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 **Supplementary Table 1**. 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 web site containing information about the most common mutations reported here can be found at: http://apps.ccge.medschl.cam.ac.uk/consortia/cimba/. This information may be periodically

updated as new data become available.

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 to undergo nonsense-mediated mRNA decay (NMD) (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 ($p<0.05$) 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 and King, 2001).

We and others have found that breast (BCCR) and ovarian (OCCR) cancer cluster regions 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.

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 **Supplementary Table 2**.

The mutational distribution among the major racial/ethnic groups and by geography are 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 Caucasian and Jews; 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 (non-founder) mutations. However, since many individuals of self-identified Jewish ancestry are 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., 2013; Weitzel, et al., 2005). 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.

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 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_69delAG 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, et al., 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, et al., 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) 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).

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. (Villarreal-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 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 socio-demographic groups are under- or over-represented or missing in our data set and, as a consequence, mutations may be over- or under-represented. 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 USA) reflect the widespread use of this testing panel in the USA 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 individuals have been tested and which centers contributed data. In particular, non-white ancestry populations are still under-represented 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 a 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 (van der Looij, et al., 2000, Ramus, et al., 1997b). 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 which 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 and Udler, 2008; Pritchard, et al., 2016), suggests that the information presented herein will also have value in genetic testing of men.

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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).

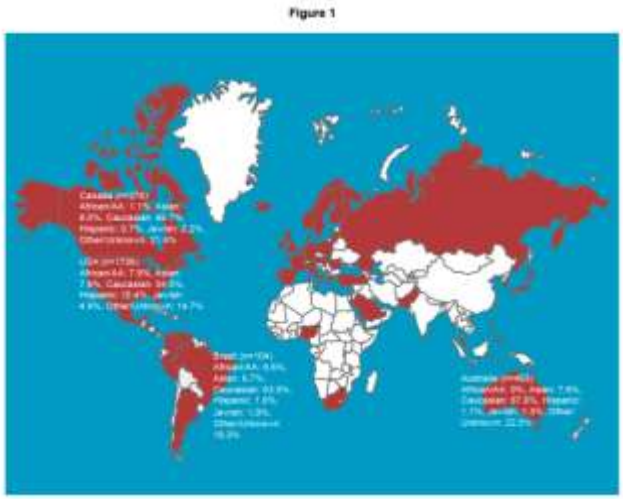

Figure 2. Proportion of Mutations in the Breast Cancer Cluster Regions (BCCR) and Ovarian Cancer Cluster Region (OCCR) in BRCA1 and BRCA2 by Ethnicity as defined previously(Rebbeck, et al., 2015). Asterisk indicates proportion is significantly different than Caucasian proportion (p-value<0.05).

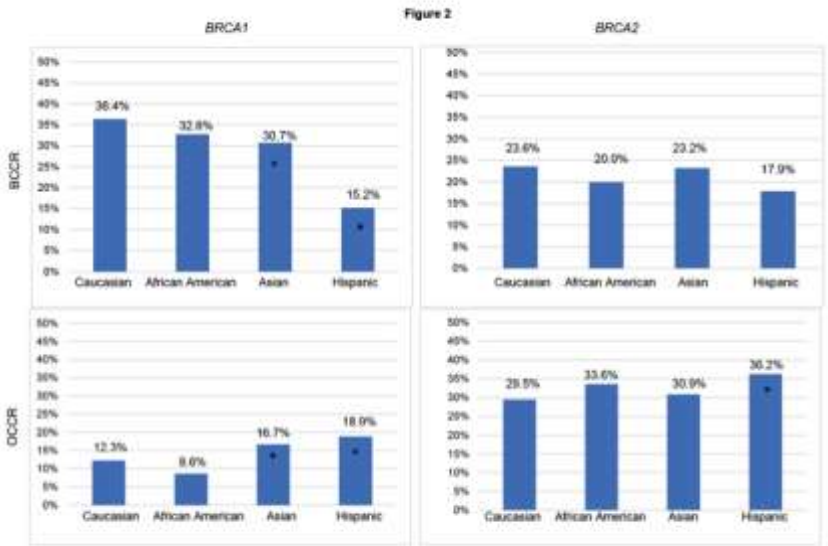

Figure 3: BRCA1 Mutation Distribution in African American, Asian, and Hispanic. Length of mutation indicator reflects the number of observed mutations. Domains are Zinc/Ring finger (green); BRCT domain (red); BRCT (C terminus) (blue). Mutation type is indicated for each mutation by color: green: missense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

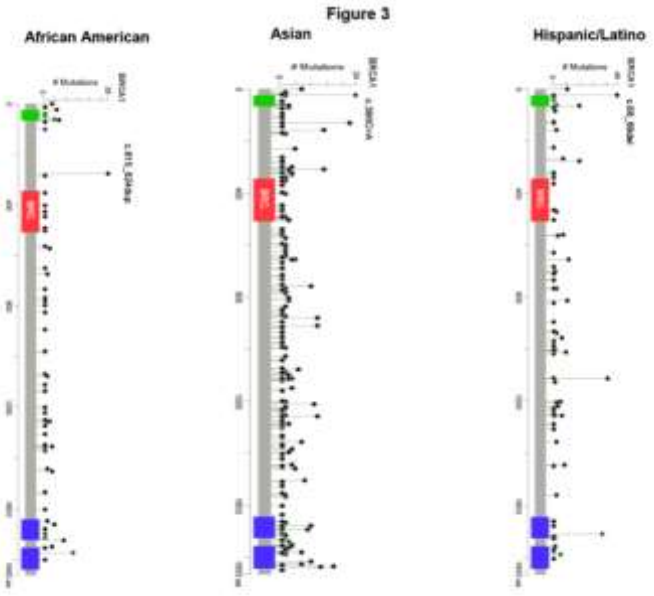

Figure 4: BRCA2 Mutation Distribution in African American, Asian, and Hispanic CIMBA Sample (per family). Length of mutation indicator reflects the number of observed mutations. Domains are BRCA repeats (green); BRCA helica (red); OB binding domain (blue); tower (yellow) and OB3 binding domain (purple). 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.

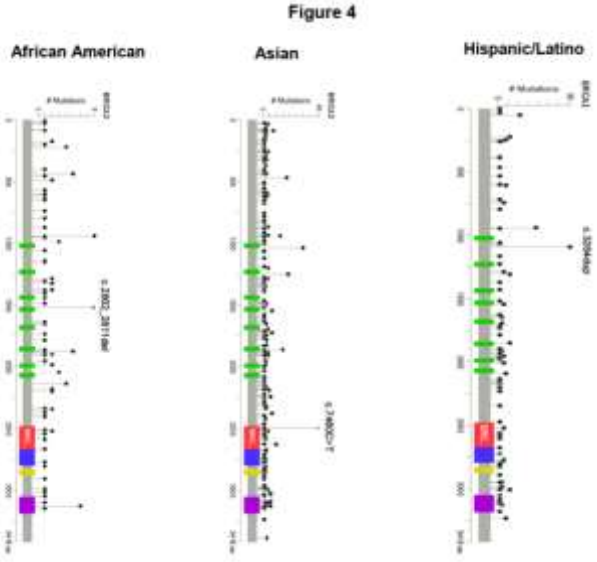

Table 1: Characteristics of *BRCA1* and *BRCA2* Mutations in the CIMBA Database (by unique mutation)

			BRCA1	(N=1,650)	*BRCA2*	(N=1,731)	p-value
	Designation	Definition	N	%	N	%	
Mutation Type	Large Deletion (DL)	Genomic DNA deletion (encompassing at least 1 exon)	130	7.9	34	1.9	<0.0001
	Large Duplication (DP)	Genomic DNA duplication (encompassing at least 1 exon)	27	1.6	11	0.6	0.010
	Frameshift (FS)	Deletion or insertion resulting in a disruption of the open reading frame	948	57.5	1,141	65.9	<0.0001
	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	0.518
	Missense (MS)	Results in an altered amino acid	46	2.8	13	0.8	0.0001
	Nonsense (NS)	Point mutation resulting in a stop codon	313	19.0	380	22.0	0.027
	Splice (SP)	Results in aberrant RNA splicing	166	10.1	131	7.6	0.013
	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	0.003
	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	<0.0001

	Unknown/Other	Unknown effect	298	18.0	183	10.6	<0.0001
Mutation Function	Nonsense-Mediated Decay (NMD)* (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	<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	<0.0001
	No RNA	Loss of expression due to deletion of promoter and/or transcription start site	21	1.3	6	0.4	0.003
	Re-Initiation	Mutations presumed to result in translation re-initiation but produce unstable protein	4	0.2	0	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	<0.0001
Mutation Class	1	Mutations predicted to be associated with unstable or no protein	1,298	78.6	1,529	88.3	<0.0001
	2	Mutations predicted to be associated with stable mutant proteins	112	6.8	36	2.1	<0.0001
	3	Unknown function	240	14.6	167	9.6	<0.0001

P-values reflect the comparison of frequencies between *BRCA1* and *BRCA2* mutation carriers.

*References (Anczukow, et al., 2008; Buisson, et al., 2006; Mikaelsdottir, et al., 2004; Perrin-Vidoz, et al., 2002; Ware, et al., 2006)

Table 2: Common *BRCA1* Mutations by Country of Origin (by family)

				Five Most Common Mutations (Number Observed)				
Conti-nent	Country	Families	Unique Mutations	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.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_3843delinsAGGC (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+4019delinsCACAG(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)	c5177_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)
	Poland	1,064	8	c.5266dup(711)	c.181T>G(276)	c.4035del(69)	c.5333-36_5406+400del(3)	.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.181T>G(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)

				Five Most Frequently Observed Mutations (Number Observed)				
Conti-nent	Country	Families	Unique Mutations	1	2	3	4	5
	Nigeria	12	9	c.1310_1313del(3)	c.8817_8820delA(2)	c.5241_5242insTA(1)	c.2402_2412del(1)	c.994del(1)
Africa	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)
	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>T5)
	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)

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(@5)	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%)	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(92)	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	