Identification of a BRCA2-Specific Modifier Locus at 6p24 Related to Breast Cancer Risk

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<td>Published Version</td>
<td>doi:10.1371/journal.pgen.1003173</td>
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Identification of a BRCA2-Specific Modifier Locus at 6p24 Related to Breast Cancer Risk


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Common genetic variants contribute to the observed variation in breast cancer risk for BRCA2 mutation carriers; those known to date have all been found through population-based genome-wide association studies (GWAS). To comprehensively identify breast cancer risk modifying loci for BRCA2 mutation carriers, we conducted a deep re-sequencing of an ongoing GWAS discovery study. Using the ranked P-values of the breast cancer associations with the imputed genotype of 1.4 M SNPs, 19,029 SNPs were selected and designed for inclusion on a custom Illumina array that included a total of 211,155 SNPs as part of a multi-consortial project. DNA samples from 3,881 breast cancer affected and 4,330 unaffected BRCA2 mutation carriers from 47 studies belonging to the Consortium of Investigators of Modifiers of BRCA1/2 were genotyped and available for analysis. We replicated previously reported breast cancer susceptibility alleles in these BRCA2 mutation carriers and for several regions (including FGR2, MAP3K1, CDKN2A/B, and PTHLH) identified SNPs that have stronger evidence of association than those previously published. We also identified a novel susceptibility allele at 6p24 that was inversely associated with breast cancer risk either in the general population or in BRCA1 mutation carriers. The locus lies within a region containing TFFAP2A, which encodes a transcriptional activation protein that interacts with several tumor suppressor genes. This report identifies the first breast cancer risk locus specific to a BRCA2 mutation background. This comprehensive update of novel and previously reported breast cancer susceptibility loci contributes to the establishment of a panel of SNPs that modify breast cancer risk in BRCA2 mutation carriers. This panel may have clinical utility for women with BRCA2 mutations weighing options for medical prevention of breast cancer.
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Funding: This work was supported by the following institutions: ICGOS: The creation of the custom Illumina multiplex chip and the genotyping of the BRCA2 carriers in CIMBA was made possible by grants from the Starr Cancer Consortium IA-A02 (PI: K Offit), the Sandra Taub Memorial Fund of the Breast Cancer Research Foundation (PI: K Offit), the Norman and Carol Stone Cancer Genetics Fund (PI: K Offit), and the European Commission's Seventh Framework Programme grant agreement 223175 (HEALTH-F2-2009-223175). AC Antoniou is a Cancer Research UK Senior Cancer Research Fellow. G Cheenneix-Trench is an NHMRC Senior Principal Research Fellow. Consortium of Modifiers of BRCA1/2 Associations: The CIMBA data management and data analysis were supported by Cancer Research UK grants U1229/11114 and C1287/A10118. S Healey is supported by an NHMRC Program Grant to G Cheenneix-Trench. AC Antoniou is a Cancer Research UK Senior Cancer Research Fellow. G Cheenneix-Trench is an NHMRC Principal Research Fellow. Amsterdam Breast Cancer Study: The ABCs study was supported by the Dutch Society Cancer (grants NKI 2007-3839; 2009-3463; BBMRI-NL, which is a Research Infrastructure financed by the Dutch government (NWO 194.021.007)); and the Dutch National Genomics Initiative. Bavarian Breast Cancer Cases and Controls: The work of the BBCS was partly funded by ELAN-Fond of the University Hospital of Erlangen. British Breast Cancer Study: The BBCS is funded by Cancer Research UK and Breastcancer.org and acknowledges NSHD funding to the NIHR Biomedical Research Centre, and the National Cancer Research Network (NCRN). Breast Cancer Family Registry Studies: The Australian Breast Cancer Family Study (ABCFS), New York (City New York Breast CCRF), Northern California Breast Cancer Family Registry (NC-BCCR), and Utah (Utah Breast CCRF) work was supported by the United States National Cancer Institute, National Institutes of Health (NIH), under RFA-CA-06-503 (P30 CA131696 and P30 ES009089), and through cooperative agreements with members of the BCCR and Principal Investigators, including Cancer Care Ontario (U01 CA69467), Columbia University (U01 CA69398), Cancer Prevention Institute of California (U01 CA69417), Fox Chase Cancer Center (U01 CA69631), Huntsman Cancer Institute (U01 CA69446), and University of Melbourne (CA69638). The ABCFS was also supported by the National Health and Medical Research Council of Australia, the New South Wales Health, the Victorian Health Promotion Foundation (Australia), and the Victorian Breast Cancer Research Consortium. The New York BCRR site was also supported by NIH grants P30 CA13696 and P30 ES009089. MC Southey is an NHMRC Senior Principal Research Fellow and a Victorian Breast Cancer Research Consortium Group Leader. Baltic Familial Breast Ovarian Cancer Consortium: BFBOCC is partly supported by: Lithuania: BFBOCC-RT, Research Council of Lithuania grant LG-19-2010, and Hereditary Cancer Association (Pavelės laisvo asociacija). Latvia: BFBOCC-EL is partly supported by the Latvian State grant 10.00.01.08 as part of a grant agreement. Estonia: BFBOCC-EE was supported by Ahkrum Foundation, Hopp Foundation, the Helmholtz Society and the German Cancer Research Center (DKFZ). Rigshospitalet: The CBCS study was supported by the NEYE Foundation, CECILE Breast Cancer Study: The CECILE study was funded by Fondation de France, Institut National du Cancer (INCa), Ligue Nationale contre le Cancer, Ligue contre le Cancer Grand Ouest, Agence Nationale de Sante´ Sante´ (ANSES), Agence Nationale de la Recherche (ANR), Copenhagen General Population Study: The COPS was supported by the Chief Physician Johan Boserup and Lise Boserup Fund, the Danish Medical Research Council and Herlev Hospital. Spanish National Cancer Centre: The CNIO work was partly supported by grants from Cancer Association for European Collaboration (ACEC008), RTICC 060002/1060, FIS/P008/1120, Mutua Madrileña Foundation (FMMA) and SAF2010-20493. Spanish National Cancer Centre Breast Cancer Study: The CNIO-BCS was supported by the Genome Spain Foundation, the Red Tematica de Investigacion Coordinativa en Cancer y grupos from the Asociación Española contra el Cancer and the Fondo de Investigación Sanitario (PI11/00293 and PI081120). City of Hope Cancer Center: The City of Hope Clinical Cancer Genetics Community Research Network is supported by Award Number R01CA153828 (PI: JW Neitzel) from the National Cancer Institute and the Office of the Director, National Institutes of Health. CONsorzio Studi ITaliani sui Tumori Ereditari Alla Mammella: CONSIT TEAM was funded by grants from Fondazione Italiana per la Ricerca sul Cancro (Special Project “Hereditary tumours”), Italian Association for Cancer Research (AIRC, IG 8713), Italian Ministry of Health (Extraordinary National Cancer Program 2006, “Alleanza contro il Cancro” and “Progetto Tumori Femminili”), Italian Ministry of Education, University and Research (Prin 2008) Centro di Ascolto Donne Operate al Seno (CAOS) association and from funds by Italian citizens who allocated the 5-1000 share of their tax payment in support of the Fondazione RICC Instituto Nazionale Tumori, according to Italian laws (INT-Institutional strategic projects “S<1000”). German Cancer Research Center: The DKFZ study was supported by the DKFZ. Genen Omgeving studie van de werkgroep Hereditair Boorlekanker Onderzoek Nederland. The DNA HEYBON study is supported by the Dutch Cancer Society grants N01198-1824, N02985- 3088, N02007-3756, the NWO grant 91109024, the Pink Ribbon grant 11005, and the BBMRI project CP46/NWO. Epidemiological study of BRCA1 & BRCA2 mutation carriers: EMBRACE is supported by Cancer Research UK Grants C1287/A10118 and C1287/A11990. DG Evans is supported by an NHRI grant to the Biomedical Research Centre, Manchester. ESTHER Breast Cancer Study: The ESTHER study was supported by a grant from the Baden Württemberg Ministry of Science, Research and Art. Additional costs were supported in the context of the VERDI study, which was supported by a grant from the German Cancer Aid (Deutsche Krebshilfe). German Consortium: German Breast Cancer: GC-HBC is supported by the German Cancer Aid (grant no 109076); by the Center for Molecular Medicine Cologne (CMMC), and by Deutsche Krebs hilfe (107 352). GC-HBC is supported by Deutsche Krebshilfe. Genetic Modifiers of cancer risk in BRCA1/2 mutation carriers: The GEMO study was supported by the Ligue Nationale contre le Cancer: the Association “Le cancer du sein, parlons-en!” Award and the Canadian Institutes of Health Research for the “CIHR Team in Familial Risks of Breast Cancer” program. Environment Gene-Environment Interaction and Breast Cancer in Germany: The GENICA was funded by the German Federal Ministry of Education and Research (BMBF) Germany grants 01WK9975/S, 01WK9978/S, 01WK9977/S and 01WK0114, the Robert Bosch Foundation, Stuttgart, Deutsches Krebsforschungszentrum (DKFZ), Heidelberg, Institute for Prevention and Occupational Medicine of the German Social Accident Insurance (DGUV) Administrative Office and Tissue Bank (CA 27469), the GOG Statistical and Data Center (CA 37517), and GOG’s Cancer Prevention and Control Committee (CA 101165). MH Greene and PL Mai are supported by funding from the Intramural Research Program, NCI. Hospital Clinico San Carlos: HCSC was supported by a grant RD06/0020/021 from RTICC (ISCIII), Spanish Ministry of Economy and Competitiveness. Helsinki Breast Cancer Study: The HEBCS was financially supported by the Helsinki University Central Hospital Research Fund, Academy of Finland (132473), the Finnish Cancer Society, the Nordic Cancer Society, and the Sigrid Juselius Foundation. Hannover-Minbak Breast Cancer Study: The HMBCS was supported by a grant from the Friends of Hannover Medical School and by the Rudolf Bartling Foundation. Study of Genetic Mutations in Breast and Ovarian Cancer patients in Hong Kong and Asia: HBRCB is supported by The Hong Kong Hereditary Breast Cancer Family Registry and the Dr. Ellen Li Charitable Foundation, Hong Kong. Molecular Genetic Studies of Breast and Ovarian Cancer in Hungary: Hungarian Breast Cancer Research Grant KTA-OTKA CK-80745 and the Norwegian EEA Financial Mechanism HU0115/ NA/008/3-OP-9. Institut Català d’Oncologia: The ICO study was supported by the Asociación Española Contra el Cancer, Spanish Health Research Foundation, Ramon Areces Foundation, Carlos III Health Institute, Catalan Health Institute, and Autonomous Government of Catalonia and contract grant numbers ISCIII RETIC RD06020201051, PI09/02483, P101/01422, P101/00748, 2009SGR2920, and 2009SQR283. Iceland Landsvirkjun-University Hospital: The ILUH group was supported by the Icelandic Association "Walking for Breast Cancer Research" and by the Landspitali University Hospital Research Fund. Interdisciplinary HEath Research Internal Team Breast Cancer susceptibility: INHERIT 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. J Simhardar is Chairholder of the Canada Cancer Research Chair in Oncogenetics. Istituto Oncologico Veneto: The IOVHBBCS study was supported by the Ministero dell’Istruzione, dell’Universita e della Ricerca (Progetto “Protezione e Genetica Femminile” and RIF: LIV/UNUSS/Cartelle ACC2/86.7”). Karolinska Breast Cancer Study: The KARBAC study was funded by the Swedish Cancer Society, the Gustav V Jubilee Foundation, and the Bert von Kanton Foundation. Kuopio Breast Cancer Project: The KBCP was financially supported by the special Government Funding (EVO) of Kuopio University
Introduction

The lifetime risk of breast cancer associated with carrying a BRCA2 mutation varies from 40 to 84% [1]. To determine whether common genetic variants modify breast cancer risk for BRCA2 mutation carriers, we previously conducted a GWAS of BRCA2 mutation carriers from the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA) [2]. Using the Affymetrix 6.0 platform, the discovery stage results were based on 899 young (<40 years) affected and 804 unaffected carriers of European ancestry. In a rapid replication stage wherein 85 discovery stage SNPs with the smallest p-values were genotyped, 12 additional BRCA2 mutation carriers, only published loci associated with breast cancer risk in the general population, including FGFR2 (rs2018118; P = 1.2 × 10^{-8}), were associated with breast cancer risk at the genome-wide significance level among BRCA2 mutation carriers.

Hospital grants, Cancer Fund of North Savo, the Finnish Cancer Organizations, the Academy of Finland, and by the strategic funding of the University of Eastern Finland. Kathleen Cunningham Consortium for Research into Familial Breast Cancer: KCoFab is supported by grants from the National Breast Cancer Foundation and the National Health and Medical Research Council (NHMRC) and by the Queensland Cancer Fund; the Cancer Council of New South Wales; Cancer Council Victoria, Tasmania, and South Australia; and the Cancer Foundation of Western Australia. G Chenexev-Trench and AB Spurdle are NHMRC Senior Research Fellows. Financial support for the AOCS was provided by the United States Army Medical Research and Materiel Command (DAMD17-01-1-0729), the Cancer Council of Tasmania and Cancer Foundation of Western Australia, and the NHMRC (199660). G Chenexev-Trench is supported by the NHMRC. The Clinical Follow Up Study (funded in 2000 by NHMRC and currently by the National Breast Cancer Foundation) is supported by the Victorian Breast Cancer Foundation. KOHRA is a grant from the National R&D Program for Cancer Control, Ministry for Health, Welfare and Family Affairs, Republic of Korea (1020330). Leuven Multidisciplinary Breast Centre: LMBC is supported by the ‘Stichting tegen Kanker’ (232-2008 and 196-2010). D Lambrecht is supported by the FWO and the KULPVT/10-016-SymBioSys. Mammary Carcinoma Risk Factor Investigation: The MARIE study was supported by the Deutsche Krebshilfe e.V. [70-0078], the Hamburg Cancer Society, the German Cancer Research Center, and the genotype work in part by the Federal Ministry of Education and Research (BMBF) Germany [01KHO6102]. Mayo Clinic: MAYO is supported by NIH grant CA128977, an NCI Specialized Program of Research Excellence (SPOR) in Breast Cancer (CA116201), a U.S. Department of Defence Ovarian Cancer Idea award (W81XWH-10-1-0341), and grants from the Breast Cancer Research Foundation and the Komen Foundation for the Cure. Milan Breast Cancer Study Group: MBCSG was funded by grants from Fondazione Italiana per la Ricerca sul Cancro Special Project “Hereditary tumors”, Italian Association for Cancer Research (AIRC, IG 8713), Italian Ministry of Health (“Progetto Tumori Femminili”), and by Italian citizens who allocated the 5 x 10^4 share of their tax payment in support of the Fondazione IRCCS Istituto Nazionale Tumori, according to Italian laws (INT-Institutional strategic projects “5 x 10^4”). Melbourne Collaborative Cohort Study: MCCS cohort recruitment was funded by VicHealth and Cancer Council Victoria. The MCCS was further supported by Australian NHMRC grants 209057, 251353 and 504711 and by infrastructure provided by Cancer Council Victoria. McGill University: The McGill Study was supported by Jewish General Hospital Weekend to End Breast Cancer, Quebec Ministry of Economic Development, Innovation and Export Trade. Multi-Ethnic Cohort: The MEC was supported by NIH grants CA63464, CA54281, CA098758, and CA132839. Memorial Sloan-Kettering Cancer Center: The MSKCC was supported by Breast Cancer Research Foundation, Niehaus Clinical Cancer Genetics Initiative, Andrew Sabin Family Foundation, and Lymphoma Foundation. Montreal Gene-Environment Breast Cancer Study: The work of MLTGENBCS was supported by the Quebec Breast Cancer Foundation, the Canadian Institutes of Health Research for the “CIHR Team in Familial Risks of Breast Cancer” program grant CRN-87521 and the Ministry of Economic Development, Innovation and Export Trade grant PSI-SIHR-701. J Simard is Chairholder of the Canada Research Chair in Oncogenetics. National Cancer Institute: The research of MH Greene and PL Mai was supported by the Intramural Research Program of the US National Cancer Institute, NIH, and by support contracts NO2-CF-10191-50 and NO2-CF-65504 with Westat, Rockville, MD. National Israeli Cancer Control Center: NICCC is supported by Clalit Health Services in Israel. Some of its activities are supported by the Israel Cancer Association and the Breast Cancer Research Foundation (BCRF), New York. N. N. Petrov Institute of Oncology: The NNPPO study has been supported by the Russian Federation for Basic Research (grants 11-04-00227, 12-04-00928, and 12-04-01490) and the Federal Agency for Science and Innovations, Russia (contract 02.740.11.0780). Oulu Breast Cancer Study: The OBCS was supported by research contracts from the Finnish Cancer Foundation, the Academy of Finland, the University of Oulu, and the University of Helsinki. Oulu University Hospital, Department of Medical Centre Breast Cancer Study: The ORIGO study was supported by the Dutch Cancer Society (RUL 1997-1505) and the Biobanking and Biomolecular Resources Research Infrastructure (BBMRI-NL CP16). The Ohio State University Comprehensive Cancer Center: OSUCCG is supported by the Ohio State University Comprehensive Cancer Center. SEABASS is supported by the Ministry of Science, Technology and Innovation, Ministry of Higher Education (U.M/C/ HIR/MOE/06) and Cancer Research Initiatives Foundation. The U.S. National Cancer Institute Polish Breast Cancer Study: The PCB5 was funded by Intermural Research Funds of the National Cancer Institute, Department of Health and Human Services, USA. Karolinska Mammography Project for Risk Prediction of Breast Cancer - prevalent cases: The PKARMA study was supported by Marit and Hans Rausings Initiative Against Breast Cancer. Rotterdam Breast Cancer Study: The RBCS was funded by the Dutch Cancer Society (DDHK 2004-3124, DDHK 2009-4318). Singapore and Sweden Breast Cancer Study: The SASBAC study was supported by funding from the Agency for Science, Technology and Research of Singapore (A*STAR), the U.S. National Institute of Health (NIH), and the Susan G. Komen Breast Cancer Foundation. Sheffield Breast Cancer Study: The SBCS was supported by Yorkshire Cancer Research Foundation S295, S299, and S305PA. South East Asian Breast Cancer Association Study: SEABASS is supported by the Ministry of Science, Technology and Innovation, Ministry of Higher Education (U.M/C/HIR/ MOE/06) and Cancer Research Initiatives Foundation. The Malaysian Breast Cancer Genetic Study is funded by research grants from the Malaysian Ministry of Science, Technology and Innovation; Ministry of Higher Education (U.M/C/HIR/MOE/06); and charitable funding from Cancer Research Initiatives Foundation. Study of Epidemiology and Risk Factors in Cancer Heredity: SEARCH is funded by programme grants from Cancer Research UK (C490/A101241/C8197/A10123). AM Dunning was funded by [C8197/A10165]. Sheba Medical Centre: The SMC study was partially funded through a grant by the Israel Cancer Association and the fund for the Israeli Inherited Breast Cancer Syndrome. Swedish Breast Cancer Study: SWE-BRCA collaborators are supported by the Swedish Cancer Society. IHCC-Szeczin Breast Cancer Study: The SZBCS was supported by Grant PBZ_KBN_122/P05/2004. The University of Chicago Center for Clinical Cancer Genetics and Global Health: UCHICAGO is supported by grants from the U.S. National Cancer Institute (NIH/NCI) and by the Ralph and Marion Falk Medical Research Trust, the Entertainment Industry Fund National Women’s Cancer Research Alliance, and the Breast Cancer Foundation. University of California Los Angeles: The UCLA study was supported by the Jonsson Comprehensive Cancer Center Foundation and the Breast Cancer Research Foundation. University of California San Francisco: The UCSF study was supported by the UCSF Cancer Risk Program and the Helen Diller Family Comprehensive Cancer Research Foundation. United Kingdom Breast突破 Generations Studies: The UKBGs is funded by Breakthrough Breast Cancer and the Institute of Cancer Research (ICR). ICR acknowledges NHS funding to the NIHR Biomedical Research Centre. United Kingdom Familial Ovarian Cancer Registries: UKFOCR was supported by a project grant from CRUK to PDP Pharoah. University of Pennsylvania: The UPENN study was supported by the National Institutes of Health (NIH) (R01-CA102776 and R01-CA117996). University of Sydney: The Sydney G. Komen Foundation, the Cure, and the Breast Cancer Australia Research Register. Victorian Breast Cancer Foundation. Victorian Familial Cancer Trials Group: The VFCTG was supported by the Victorian Cancer Agency, Cancer Australia, and the National Breast Cancer Foundation. Women’s Cancer Program: The WCP at the Samuel Oschin Comprehensive Cancer Institute is funded by the American Cancer Society Early Detection Professorship (SIOP-06-258-01-COUN). Genetic Modifiers of Cancer Risk in BRCA1/2 Mutation Carriers (GEMO) study: The study was supported in part by a ‘Ligue Nationale Contre le Cancer-‘Cancer d’hier, cancer d’aujourd’hui’ Award, and the Canadian Institutes of Health Research and the Canadian Breast Cancer Foundation for the “CIHR Team in Familial Risks of Breast Cancer” program. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

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GWAS of BRCA2 Mutation Carriers

Author Summary

Women who carry BRCA2 mutations have an increased risk of breast cancer that varies widely. To identify common genetic variants that modify the breast cancer risk associated with BRCA2 mutations, we have built upon our previous work in which we examined genetic variants across the genome in relation to breast cancer risk among BRCA2 mutation carriers. Using a custom genotyping platform with 211,155 genetic variants known as single nucleotide polymorphisms (SNPs), we genotyped 3,881 women who had breast cancer and 4,330 women without breast cancer, which represents the largest possible, international collection of BRCA2 mutation carriers. We identified that a SNP located at 6p24 in the genome was associated with lower risk of breast cancer. Importantly, this SNP was not associated with breast cancer in BRCA1 mutation carriers or in a general population of women, indicating that the breast cancer association with this SNP might be specific to BRCA2 mutation carriers. Combining this BRCA2-specific SNP with 13 other breast cancer risk SNPs also known to modify risk in BRCA2 mutation carriers, we were able to derive a risk prediction model that could be useful in helping women with BRCA2 mutations weigh their risk-reduction strategy options.

Materials and Methods

Ethics statement
Each of the host institutions (Table S1) recruited under ethically-approved protocols. Written informed consent was obtained from all subjects.

Study subjects
The majority of BRCA2 mutation carriers were recruited through cancer genetics clinics and some came from population or community-based studies. Studies contributing DNA samples to these research efforts were members of the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA) with the exception of one study (NICCC). Eligible subjects were women of European descent who carried a pathogenic BRCA2 mutation, had complete phenotype information, and were at least 18 years of age. Harmonized phenotypic data included year of birth, age at cancer diagnosis, age at bilateral prophylactic mastectomy and oophorectomy, age at interview or last follow-up, BRCA2 mutation description, self-reported ethnicity, and breast cancer estrogen receptor status.

GWAS discovery stage samples. Details of these samples have been described previously [2]. Data from 899 young (<40 years) affected and 804 older (>40 years) unaffected carriers of European ancestry from 14 countries were used to select SNPs for inclusion on the iCOGS array.

Samples genotyped in the extended replication set. Forty-seven studies from 24 different countries (including two East-Asian countries) provided DNA from a total of 10,048 BRCA2 mutation carriers. All eligible samples were genotyped using COGs, including those from the discovery stage.

Genotyping and quality control
BRCA2 SNP selection for inclusion on iCOGS. The Collaborative Oncological Gene-Environment Study (COGS) consortium developed a custom genotyping array (referred to as the iCOGS array) to provide efficient genotyping of common and rare genetic variants to identify novel loci that are associated with risk of breast, ovarian, and prostate cancers as well as to fine-map known cancer susceptibility loci. SNPs were selected for inclusion on iCOGS separately by each participating consortium: Breast Cancer Association Consortium (BCAC) [6], Ovarian Cancer Association Consortium (OCAC) [7], Prostate Cancer Association Group to Investigate Cancer Associated Alterations in the Genome (PRACTICAL) [8], and CIMBA. SNP lists from a BRCA2 GWAS and SNPs in candidate regions were used together with the BRCA2 GWAS lists to generate a ranked CIMBA SNP list that included SNPs with the following nominal proportions: 55.5% from the BRCA1 GWAS, 41.6% from the BRCA2 GWAS and fine mapping, 2.9% for CIMBA candidate SNPs. Each consortium was given a share of the array: nominally 25% of the SNPs each for BCAC, PRACTICAL and OCAC; 17.5% for CIMBA; and 7.5% for SNPs from commonly researched pathways (e.g., inflammation). For the CIMBA BRCA2 GWAS, we used the iCOGS array as the platform to genotype the extended replication set of the discovery GWAS stage [2]. SNPs were selected on the basis of the strength of their associations with breast cancer risk in the discovery stage [2], using imputed genotype data for 1.4 M SNPs identified through CEU+TSI samples on HapMap3, release 2. A ranked list of SNPs was based on the 1-df trend test statistic, after excluding highly correlated SNPs (r^2>0.4). The final list included the 39,015 SNPs with the smallest p-values. An additional set of SNPs were selected for fine mapping of the regions surrounding the SNPs found to be associated with breast cancer in the discovery GWAS stage: rs16917302 on 10q21 and a locus on 20q13 (rs311499), were also associated with breast cancer risk in BRCA2 mutation carriers with P-values<10^{-4} (P = 3.8x10^{-5} and 6.6x10^{-5}, respectively). A nearby SNP in ZNF365 was also associated with breast cancer risk in a study of unselected cases [3] and in a study of mammographic density [4]. Additional follow-up replicated the findings for rs16917302, but not rs311499 in a larger set of BRCA2 mutation carriers. To seek additional breast cancer risk modifying loci for BRCA2 mutation carriers, we conducted an extended replication of the GWAS discovery results in a larger set of BRCA2 mutation carriers in CIMBA, which represents the largest, international collection of BRCA2 mutation carriers.

mutation carriers. Two other loci, in ZNF365 (rs16917302) on 10q21 and a locus on 20q13 (rs311499), were also associated with breast cancer risk in BRCA2 mutation carriers with P-values<10^{-4} (P = 3.8x10^{-5} and 6.6x10^{-5}, respectively). A nearby SNP in ZNF365 was also associated with breast cancer risk in a study of unselected cases [3] and in a study of mammographic density [4]. Additional follow-up replicated the findings for rs16917302, but not rs311499 in a larger set of BRCA2 mutation carriers. Combining this BRCA2-specific SNP with 13 other breast cancer risk SNPs also known to modify risk in BRCA2 mutation carriers, we were able to derive a risk prediction model that could be useful in helping women with BRCA2 mutations weigh their risk-reduction strategy options.

Genotyping. The genotyping was performed on DNA samples from 10,048 BRCA2 mutation carriers at the McGill University and Génome Québec Innovation Centre (Montreal, Canada). As a quality control measure, each plate included DNA samples from six individuals who were members of two CEPH trios. Some plates also contained three duplicate pairs of quality control samples. Genotypes were called using GenCall [9]. Initial calling was based on a cluster file generated using 270 samples from Hapmap2. To generate the final calls, we first selected a subset of 3,018 individuals, including samples from each of the genotyping centers in the iCOGS project, each of the participating...
consortia, and each major ethnicity. Only plates with a consistent high call rate in the initial calling were used. We also included 300 samples of European, African, and Asian ethnicity genotyped as part of the Hapmap and 1000 Genomes project, and 160 samples that were known positive controls for rare variants on the array. This subset was used to generate a cluster file that was then applied to call the genotypes for the remaining samples.

**Quality control of SNPs.** Of the 211,155 SNPs on the iCOGS array, we excluded SNPs for the following reasons (Table S2): on the Y-chromosome, call rate <95%, deviations from Hardy-Weinberg equilibrium (P<10^-5), using a stratified 1-d.f. test [10], and monomorphic SNPs. That gave discrepant genotypes among known duplicates were also excluded. After quality control filtering, 200,908 SNPs were available for analysis (Table S2); 18,086 of which were selected on the basis of the discovery BRCA2 GWAS [2]. Cluster plots of all reported SNPs were inspected manually for quality (Figure S1).

**Description of imputation.** Genotypes for SNPs identified through the 1000 Genomes Phase I data (released Jan 2012) [11] were imputed using SNPs on the iCOGS chip in a region of 500 kb around the novel modifier locus at 6p24. The boundaries were determined according to the linkage disequilibrium (LD) structure in the region based on HapMap data. The imputation was carried out using IMPUTE 2.2 [12]. SNPs with imputation information/accuracy r^2>0.30 were excluded in the analyses.

**Quality control of DNA samples.** Of 10,048 genotyped samples (Table S2), 742 were excluded because they did not meet the phenotypic eligibility criteria or had self-reported non-CEU ethnicity. Samples were then excluded for the following reasons: on the Y-chromosome, call rate <95%, low or high heterozygosity (P<10^-5), discordant genotypes from previous CIBA genotyping efforts, or discordant duplicate samples. For duplicates with concordant phenotypic data, or in cases of cryptic monozygotic twins, only one of the samples was included. Cryptic duplicates for which phenotypic data indicated different individuals were all excluded. Samples of non-European ancestry were identified using multi-dimensional scaling, after combining the BRCA2 mutation carriers with the HapMap2 CEU, CHB, JPT and YRI samples using a set of 37,120 uncorrelated SNPs from the iCOGS array. Samples with >19% non-European ancestry were excluded (Figure S2). A total of 4,330 affected and 3,881 unaffected BRCA2 carrier women of European ancestry from 42 studies remained in the analysis (Table S1), including 3,234 breast cancer cases and 3,490 unaffected carriers that were not in the discovery set.

**BRCA1 and BCAC samples.** Details of the sample collection, genotyping and quality control process for the BRCA1 and BCAC samples, are reported elsewhere [13,14].

**Statistical methods**

The associations between genotype and breast cancer risk were analyzed within a retrospective cohort framework with time to breast cancer diagnosis as the outcome [15]. Each BRCA2 carrier was followed until the first event: breast or ovarian cancer diagnosis, bilateral prophylactic mastectomy, or age at last observation. Only those with a breast cancer diagnosis were considered as cases in the analysis. The majority of mutation carriers were recruited through genetic counseling centers where genetic testing is targeted at women diagnosed with breast or ovarian cancer and in particular to those diagnosed with breast cancer at a young age. Therefore, these women are more likely to be sampled compared to unaffected mutation carriers or carriers diagnosed with the disease at older ages. As a consequence, sampling was not random with respect to disease phenotype and standard methods of survival analysis (such as Cox regression) may lead to biased estimates of the associations [16]. We therefore conducted the analysis by modelling the retrospective likelihood of the observed genotypes conditional on the disease phenotypes. This has been shown to provide unbiased estimates of the associations [15]. The implementation of the retrospective likelihoods has been described in detail elsewhere [15,17]. The associations between genotype and breast cancer risk were assessed using the degree of freedom score test statistic based on the retrospective likelihood [15]. In order to account for non-independence between relatives, an adjusted version of the score test was used in which the variance of the score was derived taking into account the correlation between the genotypes [18]. P-values were not adjusted using genomic control because there was little evidence of inflation. Inflation was assessed using the genomic inflation factor, λ. Since this estimate is dependent on sample size, we also calculated λ adjusted to 1000 affected and 1000 unaffected samples. Per-allele and genotype-specific hazard-ratios (HR) and 95% confidence intervals (CI) were estimated by maximizing the retrospective likelihood. Calendar-year and cohort-specific breast cancer incidences for BRCA2 were used [1]. All analyses were stratified by country of residence. The USA and Canada strata were further subdivided by self-reported Ashkenazi Jewish ancestry. The assumption of proportional hazards was assessed by fitting a model that included a genotype-by-age interaction term. Between-country heterogeneity was assessed by comparing the results of the main analysis to a model with country-specific log-HRs. A possible survival bias due to inclusion of prevalent cases was evaluated by re-fitting the model after excluding affected carriers that were diagnosed ≥5 years prior to study recruitment. The associations between genotypes and tumor subtypes were evaluated using an extension of the retrospective likelihood approach that models the association with two or more subtypes simultaneously [19]. To investigate whether any of the significant SNPs were associated with ovarian cancer risk for BRCA2 mutation carriers and whether the inclusion of ovarian cancer patients as unaffected subjects biased our results, we also analyzed the data within a competing risks framework and estimated HR simultaneously for breast and ovarian cancer using the methods described elsewhere [15]. Analyses were carried out in R using the GenABEL libraries [20] and custom-written software. The retrospective likelihood was modeled in the pedigree-analysis software MENDEL [21], as described in detail elsewhere [15].

**TCGA analysis.** Affymetrix SNP 6.0 genotype calls for normal (non-tumor) breast DNA were downloaded for all available individuals from The Cancer Genome Atlas in September 2011. Analyses were limited to the 401 individuals of European ancestry based on principal component analysis. Expression levels in breast tumor tissue were adjusted for the top two principal components, age, gender (there are some male breast cancer cases in TCGA), and average copy number across the gene in the tumor. Linear regression was then used to test for association between the SNP and the adjusted gene expression level for all genes within one megabase.

**Gene set enrichment analysis.** To investigate enrichment of genes associated with breast cancer risk, the gene-set enrichment approach was implemented using Versatile Gene-based Association Study [22] based on the ranked P-values from retrospective likelihood analysis. Association List Go Annotator was also used to prioritize gene pathways using functional annotation from gene ontology (GO) [23] to increase the power to detect association to a pathway, as opposed to individual genes in the pathway. Both analyses were corrected for LD between SNPs, variable gene size, and interdependence of GO categories.
where applicable, based on imputation. 100,000 Monte Carlo simulations were performed in VEGAS and 5000 replicate gene lists using random sampling of SNPs and 5000 replicate studies (sampling with replacement) were performed to estimate P-values.

**Predicted absolute breast cancer risks by combined SNP profile.** We estimated the absolute risks of developing breast cancer based on the joint distribution of SNPs associated with breast cancer for BRCA2 mutation carriers. The methods have been described elsewhere [24]. To construct the SNP profiles, we considered the single SNP from each region with the strongest evidence of association in the present dataset. We included all loci that had previously been found to be associated with breast cancer risk through GWAS in the general population and demonstrated associations with breast cancer risk for BRCA2 mutation carriers, and loci that had GWAS level of significance in the current study.

We assumed that all loci in the profile were independent (i.e. they interact multiplicatively on BRCA2 breast cancer risk). Genotype frequencies were obtained under the assumption of Hardy-Weinberg Equilibrium. For each SNP, the effect of each allele was assumed to be consistent with a multiplicative model (log-additive). We assumed that the average, age-specific breast cancer incidences, over all associated loci, agreed with published breast cancer risk estimates for BRCA2 mutation carriers [1].

**Results**

The genomic inflation factor (λ) based on the 18,086 BRCA2 GWAS SNPs in the 6,724 BRCA2 mutation carriers who were not used in the SNP discovery set was 1.034 (λ adjusted to 1000 affected and 1000 unaffected: 1.010, Figure S3). Multiple variants were associated with breast cancer risk in the combined discovery and replication datasets (Figure S4). SNPs in three independent regions had P-values<5×10⁻⁸; one was a region not previously associated with breast cancer.

The most significant associations were observed for known breast cancer susceptibility regions, rs2420946 (per allele P = 2×10⁻¹⁴) in FGFR2 and rs3803662 (P = 5.4×10⁻¹¹) near TOX3 (Table 1). Breast cancer risk associations with other SNPs reported previously for BRCA2 mutation carriers are summarized in Table 1. In this larger set of BRCA2 mutation carriers, we also identified novel SNPs in the 12p11 (PTHLH), 5q11 (MAFK1), and 9p21 (CDK2A1/B) regions with smaller P-values for association than those of previously reported SNPs. These novel SNPs were not correlated with the previously reported SNPs (r²<0.14). For one of the novel SNPs identified in the discovery GWAS [2], ZNF363 rs16917302, there was weak evidence of association with breast cancer risk (P = 0.01); however, an uncorrelated SNP, rs17221319 (r²<0.01), 54 kb upstream of rs16917302 had stronger evidence of association (P = 6×10⁻⁸).

One SNP, rs9348512 at 6p24 not known to be associated with breast cancer, had a combined P-value of association of 3.9×10⁻⁸ amongst all BRCA2 samples (Table 2), with strong evidence of replication in the set of BRCA2 samples that were not used in the discovery stage (P = 5.2×10⁻⁴). The minor allele of rs9348512 (MAF = 0.35) was associated with a 15% decreased risk of breast cancer among BRCA2 mutation carriers (per allele HR = 0.85, 95% CI 0.80–0.90) with no evidence of between-country heterogeneity (P = 0.78, Figure S5). None of the genotype (n = 68) or imputed (n = 3,307) SNPs in this region showed a stronger association with risk (Figure 1; Table S3), but there were 40 SNPs with P<10⁻⁴ (pairwise r²>0.38 with rs9348512, with the exception of rs11526201 for which r² = 0.01, Table S3). The association with rs9348512 did not differ by 6174dIT mutation status (P for difference = 0.33), age (P = 0.39), or estrogen receptor (ER) status of the breast tumor (P = 0.41). Exclusion of prevalent breast cancer cases (n = 1,732) produced results (HR = 0.83, 95% CI 0.77–0.89, P = 3.40×10⁻⁷) consistent with those for all cases.

SNPs in two additional regions had P-values<10⁻⁷ for breast cancer risk associations for BRCA2 mutation carriers (Table 2). The magnitude of associations for both SNPs was similar in the discovery and second stage samples. In the combined analysis of all samples, the minor allele of rs619373, located in FGFR3 (Xq26.3), was associated with higher breast cancer risk (HR = 1.30, 95% CI 1.17–1.45, P = 3.1×10⁻⁶). The minor allele of rs184577, located in CIP1B-A517 (2p22–p21), was associated with lower breast cancer risk (HR = 0.93, 95% CI 0.79–0.91, P = 3.6×10⁻⁶). These findings were consistent across countries (P for heterogeneity between country strata = 0.39 and P = 0.30, respectively; Figure S6). There was no evidence that the HR estimates for rs619373 and rs184577 change with age of the BRCA2 mutation carriers (P for the genotype-age interaction = 0.80 and P = 0.40, respectively) and no evidence of survival bias for either SNP (rs619373: HR = 1.35, 95% CI 1.20–1.53, P = 1.5×10⁻⁶ and rs184577: HR = 0.86, 95% CI 0.79–0.93, P = 2.0×10⁻⁴, after excluding prevalent cases). The estimates for risk of ER-negative and ER-positive breast cancer were not significantly different (P for heterogeneity between tumor subtypes = 0.79 and 0.67, respectively). When associations were evaluated under a competing risks model, there was no evidence of association with ovarian cancer risk for SNPs rs9348512 at 6p24, rs619373 in FGFR3 or rs184577 at 2p22 and the breast cancer associations were virtually unchanged (Table S4).

Gene set enrichment analysis confirmed that strong associations exist for known breast cancer susceptibility loci and the novel loci identified here (gene-based P<1×10⁻⁵). The pathways most strongly associated with breast cancer risk that contained statistically significant SNPs included those related to ATP binding, organ morphogenesis, and several nucleotide bindings (pathway-based P<0.05).

To begin to determine the functional effect of rs9348512, we examined associations of expression levels of any nearby gene in breast tumors with the minor A allele. Using data from The Cancer Genome Atlas, we found that the A allele of rs9348512 was strongly associated with mRNA levels of GCNT2 in breast tumors (Pearson's r = 7.3×10⁻⁵). The hazard ratios for the percentiles of the combined genotype distribution of loci associated with breast cancer risk in BRCA2 mutation carriers were translated into absolute breast cancer risks under the assumption that SNPs interact multiplicatively. Based on our results for SNPs in FGFR2, TOX3, 12p11, 5q11, CDK2A1/B, ESP1, 8q24, ESR1, ZNF365, 3p24, 12q24, 5p12, 11q13 and also the 6p24 locus, the 5% of the BRCA2 mutation carriers at lowest risk were predicted to have breast cancer risks by age 80 in the range of 21–47% compared to 83–100% for the 5% of mutation carriers at highest risk on the basis of the combined SNP profile distribution (Figure 2). The breast cancer risk by age 50 was predicted to be 4–11% for the 5% of the carriers at lowest risk compared to 29–81% for the 5% at highest risk.

**Discussion**

In the largest assemblage of BRCA2 mutation carriers, we identified a novel locus at 6q24 that is associated with breast cancer risk, and noted two potential SNPs of interest at Xq26 and 2p22. We also replicated associations with known breast cancer susceptibility SNPs previously reported in the general population and in BRCA2 mutation carriers. For the 12p11 (PTHLH), 5q11 (MAFK1), and 9p21 (CDK2A1/B), we found uncorrelated SNPs.
Table 1. Per allele hazard ratios (HR) and 95% confidence intervals (CI) of previously published breast cancer loci among BRCA2 mutation carriers from previous reports and from the iCOGS array, ordered by statistical significance of the region.

<table>
<thead>
<tr>
<th>Chr (Nearby Genes)</th>
<th>Report Status</th>
<th>SNP</th>
<th>r²</th>
<th>MinorAllele</th>
<th>Previously Reported Results</th>
<th>iCOGS Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ref</td>
<td>Affected N</td>
</tr>
<tr>
<td>10q26 (FGFR2)</td>
<td>reported</td>
<td>n2981575</td>
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<td>[2]</td>
<td>2,155</td>
<td>2,016</td>
</tr>
<tr>
<td></td>
<td>novel</td>
<td>n2420946</td>
<td>0.96</td>
<td>A</td>
<td>4,328</td>
<td>3,877</td>
</tr>
<tr>
<td>16q12 (TOX3)</td>
<td>reported</td>
<td>n3803662</td>
<td>A</td>
<td>[2]</td>
<td>2,162</td>
<td>2,026</td>
</tr>
<tr>
<td></td>
<td>novel</td>
<td>n10771399</td>
<td>G</td>
<td>[34]</td>
<td>3,798</td>
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</tr>
<tr>
<td>12p11 (PTHLH)</td>
<td>reported</td>
<td>n27633</td>
<td>0.05</td>
<td>C</td>
<td>4,252</td>
<td>3,841</td>
</tr>
<tr>
<td></td>
<td>novel</td>
<td>n889312</td>
<td>C</td>
<td>[24]</td>
<td>2,840</td>
<td>2,282</td>
</tr>
<tr>
<td>5q11 (MAP3K1)</td>
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<td>A</td>
<td>[34]</td>
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<td>3,316</td>
</tr>
<tr>
<td></td>
<td>novel</td>
<td>n10956163</td>
<td>0.00</td>
<td>A</td>
<td>4,329</td>
<td>3,880</td>
</tr>
<tr>
<td>11p15 (LSPI1)</td>
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<td>[24]</td>
<td>3,266</td>
<td>2,636</td>
</tr>
<tr>
<td></td>
<td>novel</td>
<td>n13281615</td>
<td>G</td>
<td>[24]</td>
<td>3,338</td>
<td>2,723</td>
</tr>
<tr>
<td>8q24</td>
<td>novel</td>
<td>n4733664</td>
<td>0.00</td>
<td>A</td>
<td>4,329</td>
<td>3,879</td>
</tr>
<tr>
<td>20q13</td>
<td>reported</td>
<td>n3114982</td>
<td>A</td>
<td>[5]</td>
<td>3,808</td>
<td>3,318</td>
</tr>
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<td>n13039229</td>
<td>0.00</td>
<td>C</td>
<td>4,326</td>
<td>3,877</td>
</tr>
<tr>
<td>6q25 (ESRT1)</td>
<td>reported</td>
<td>n59397435</td>
<td>G</td>
<td>[35]</td>
<td>3,809</td>
<td>3,316</td>
</tr>
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<td>novel</td>
<td>n2253407</td>
<td>0.01</td>
<td>A</td>
<td>4,330</td>
<td>3,881</td>
</tr>
<tr>
<td>10q21 (ZNF365)</td>
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<td>n16917302</td>
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<td>[5]</td>
<td>3,807</td>
<td>3,315</td>
</tr>
<tr>
<td></td>
<td>novel</td>
<td>n17221319</td>
<td>0.00</td>
<td>A</td>
<td>4,330</td>
<td>3,881</td>
</tr>
<tr>
<td>3p24 (SLC4A7, NEX10)</td>
<td>reported</td>
<td>n4973768</td>
<td>A</td>
<td>[24]</td>
<td>3,370</td>
<td>2,783</td>
</tr>
<tr>
<td></td>
<td>novel</td>
<td>n12920171</td>
<td>A</td>
<td>[34]</td>
<td>2,530</td>
<td>2,342</td>
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<tr>
<td>5p12</td>
<td>reported</td>
<td>n10941679</td>
<td>G</td>
<td>[24]</td>
<td>3,263</td>
<td>2,591</td>
</tr>
<tr>
<td></td>
<td>reported</td>
<td>n614367</td>
<td>A</td>
<td>[34]</td>
<td>3,789</td>
<td>3,307</td>
</tr>
<tr>
<td>1p11 (NOTCH2)</td>
<td>reported</td>
<td>n11249433</td>
<td>G</td>
<td>[35]</td>
<td>3,423</td>
<td>2,827</td>
</tr>
<tr>
<td></td>
<td>reported</td>
<td>n8504950</td>
<td>A</td>
<td>[24]</td>
<td>3,401</td>
<td>2,813</td>
</tr>
<tr>
<td>17q23 (STK34P, COX11)</td>
<td>reported</td>
<td>n8170</td>
<td>A</td>
<td>[5]</td>
<td>3,665</td>
<td>3,086</td>
</tr>
<tr>
<td></td>
<td>reported</td>
<td>n13387041</td>
<td>G</td>
<td>[24]</td>
<td>3,300</td>
<td>2,646</td>
</tr>
<tr>
<td>9q31</td>
<td>reported</td>
<td>n865686</td>
<td>C</td>
<td>[34]</td>
<td>3,799</td>
<td>3,312</td>
</tr>
<tr>
<td>10q22 (ZMIZ1)</td>
<td>reported</td>
<td>n704010</td>
<td>A</td>
<td>[34]</td>
<td>3,761</td>
<td>3,279</td>
</tr>
</tbody>
</table>

1 Reporting status of the SNP is either previously reported or novel to this report.
2 p-value was calculated based on the 1-degree of freedom score test statistic.
3 Stronger associations were originally reported for the SNP, assuming a dominant or recessive model of the ‘risk allele’. doi:10.1371/journal.pgen.1003173.t001
Table 2. Breast cancer hazard ratios (HR) and 95% confidence intervals (CI) of novel breast cancer loci with P-values of association < 10\(^{-5}\) among BRCA2 mutation carriers.

<table>
<thead>
<tr>
<th>SNP rs No. Chr (Nearby Genes)</th>
<th>Discovery Stage</th>
<th>Stage 2</th>
<th>Combined</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Genotype</td>
<td>Affected No. (%)</td>
<td>Unaffected No. (%)</td>
</tr>
<tr>
<td>rs9348512 Chr6 (TFAP2A, C6orf218)</td>
<td>CC</td>
<td>390 (46.4)</td>
<td>248 (38.3)</td>
</tr>
<tr>
<td></td>
<td>CA</td>
<td>368 (43.8)</td>
<td>299 (46.2)</td>
</tr>
<tr>
<td></td>
<td>AA</td>
<td>82 (9.8)</td>
<td>100 (15.5)</td>
</tr>
<tr>
<td></td>
<td>per allele</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs619373 ChrX (FGF13)</td>
<td>GG</td>
<td>693 (75.8)</td>
<td>568 (87.8)</td>
</tr>
<tr>
<td></td>
<td>GA</td>
<td>143 (15.7)</td>
<td>78 (12.1)</td>
</tr>
<tr>
<td></td>
<td>AA</td>
<td>4 (0.5)</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td></td>
<td>per allele</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs184577 Chr2 (C2orf58)</td>
<td>GG</td>
<td>520 (61.9)</td>
<td>368 (56.9)</td>
</tr>
<tr>
<td></td>
<td>GA</td>
<td>278 (33.1)</td>
<td>234 (36.2)</td>
</tr>
<tr>
<td></td>
<td>AA</td>
<td>42 (5.0)</td>
<td>45 (7.0)</td>
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<tr>
<td></td>
<td>per allele</td>
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</tbody>
</table>

\(^1\)P-value was calculated based on the 1-degree of freedom score test.
doi:10.1371/journal.pgen.1003173.t002
that had stronger associations than the originally identified SNP in the breast cancer susceptibility region that should be replicated in the general population. In BRCA2 mutation carriers, evidence for a breast cancer association with genetic variants in PTHLH has been restricted previously to ER-negative tumors [25]; however, the novel susceptibility variant we reported here was associated with risk of ER+ and ER− breast cancer.

The novel SNP rs9348512 (6p24) is located in a region with no known genes (Figure 1). C6orf218, a gene encoding a hypothetical protein LOC221718, and a possible tumor suppressor gene, TFAP2A, are within 100 kb of rs9348512. TFAP2A encodes the AP-2α transcription factor that is normally expressed in breast ductal epithelium nuclei, with progressive expression loss from normal, to ductal carcinoma in situ, to invasive cancer [26,27]. AP-2α also acts as a tumor suppressor via negative regulation of MYC [28] and augmented p53-dependent transcription [29]. However, the minor allele of rs9348512 was not associated with gene expression changes of TFAP2A in breast cancer tissues in The Cancer Genome Atlas (TCGA) data; this analysis might not be informative since expression of TFAP2A in invasive breast tissue is low [26,27]. Using the TCGA data and a 1 Mb window, expression changes with genotypes of rs9348512 were observed for GCNT2, the gene encoding the enzyme for the blood group I antigen glucosaminyl (N-acetyl) transferase 2. GCNT2, recently found to be overexpressed in highly metastatic breast cancer cell lines [30] and basal-like breast cancer [31], interacts with TGF-β to promote epithelial-to-mesenchymal transition, enhancing the metastatic potential of breast cancer [31]. An assessment of alterations in expression patterns in normal breast tissue from BRCA2 mutation carriers by genotype are needed to further evaluate the functional implications of rs9348512 in the breast tumorigenesis of BRCA2 mutation carriers.

To determine whether the breast cancer association with rs9348512 was limited to BRCA2 mutation carriers, we compared results to those in the general population genotyped by BCAC and to BRCA1 mutation carriers in CIMBA. No evidence of an association between rs9348512 and breast cancer risk was observed in the general population (OR = 1.00, 95% CI 0.98–1.02, P = 0.74) [14], nor in BRCA1 mutation carriers (HR = 0.99, 95% CI 0.94–1.04, P = 0.75) [13]. Stratifying cases by ER status, there was no association observed with ER-subtypes in either the general population or among BRCA1 mutation carriers (BCAC: ER positive P = 0.89 and ER negative P = 0.60; CIMBA BRCA1: P = 0.49 and P = 0.99, respectively). For the two SNPs associated with breast cancer with P < 5 × 10^{-8}, neither rs619373, located in FGF13 (Xq26.3), nor rs184577, located in CYP1B1-AS1 (2p22-p21), was associated with breast cancer risk in the general population [14] or among BRCA1 mutation carriers [13]. The narrow CIs for the overall associations in the general population and in BRCA1 mutation carriers rule out associations of magnitude similar to those observed for BRCA2 mutation carriers. The consistency of the association in the discovery and replication stages and by country, the strong quality control measures and filters, and the clear cluster plot for rs9348512 suggest that our results constitute the discovery of a novel breast cancer susceptibility locus specific to BRCA2 mutation carriers rather than a false positive finding. Replicating this SNP in an even larger population of BRCA2 mutation carriers would be ideal, but not currently possible.

Figure 1. Associations between SNPs in the region surrounding rs9348512 on chromosome 6 and breast cancer risk. Results based on imputed and observed genotypes. The blue spikes indicate the recombination rate at each position. Genotyped SNPs are represented by diamonds and imputed SNPs are represented by squares. Color saturation indicates the degree of correlation with the SNP rs9348512. doi:10.1371/journal.pgen.1003173.g001
Figure 2. Predicted breast cancer risks for BRCA2 mutation carriers by the combined SNP profile distributions. Based on the known breast cancer susceptibility loci at FGFR2, TOX3, 12p11, 5q11, CDKN2A/B, LSP1, 8q24, ESR1, ZNF365, 3p24, 12q24, 5p12, 11q13 and the newly identified BRCA2 modifier locus at 6p24. The figure shows the risks at the 5th and 95th percentiles of the combined genotyped distribution as well as minimum, maximum and average risks. doi:10.1371/journal.pgen.1003173.g002

possible because we know of no investigators with appropriate data and germline DNA from BRCA2 mutation carriers who did not contribute their mutation carriers to iCOGS. However, CIMBA studies continue to recruit individuals into the consortium.

rs9348512 (6p24) is the first example of a common susceptibility variant identified through GWAS that modifies breast cancer risk specifically in BRCA2 mutation carriers. Previously reported BRCA2-modifying alleles for breast cancer, including those in FGFR2, TOX3, MAP3K1, LSP1, 2q35, SLC4A7, 5p12, 1p11.2, ZNF365, and 19p13.1 (ER-negative only) [18,32,33], are also associated with breast cancer risk in the general population and/or BRCA1 mutation carriers. Knowledge of the 6p24 locus might provide further insights into the biology of breast cancer development in BRCA2 mutation carriers. Additional variants that are specific modifiers of breast cancer risk in BRCA2 carriers may yet be discovered; their detection would require assembling larger samples of BRCA2 mutation carriers in the future.

While individually each of the SNPs associated with breast cancer in BRCA2 mutation carriers are unlikely to be used to guide breast cancer screening and risk-reducing management strategies, the combined effect of the general and BRCA2-specific breast cancer susceptibility SNPs might be used to tailor manage subsets of BRCA2 mutation carriers. Taking into account all loci associated with breast cancer risk in BRCA2 mutation carriers from the current analysis, including the 6p24 locus, the 5% of the BRCA2 mutation carriers at lowest risk were predicted to have breast cancer risks by age 80 in the range of 21–47% compared to 83–100% for the 5% of mutation carriers at highest risk on the basis of the combined SNP profile distribution. These results might serve as a stimulus for prospective trials of the clinical utility of such modifier panels.

Supporting Information

Table S1 Quality control filtering steps for BRCA2 mutation carriers and SNPs on the COGs array.

Table S2 Description of breast cancer affected and unaffected BRCA2 carriers included in the final analysis of the COGs array SNPs.

Table S3 Breast cancer hazards ratios (HR) and 95% confidence intervals for all SNPs with P<10^{-5} in a 500 Mb region around rs9348512 on 6p24 among BRCA2 mutation carriers.

Table S4 Associations with SNPs at 6p24, FGFI3 and 2p22 and breast and ovarian cancer risk using a competing risk analysis model.

Acknowledgments

iCOGS: We acknowledge the contributions of Kyrilaki Michailidou, Jonathan Tyrer, and Ali Amin Al Olama to the iCOGS statistical analyses and Shahana Ahmed, Melanie J. Maranian, and Catherine S. Healey for their contributions to the iCOGS genotyping quality control process.

Consortium of Modifiers of BRCA1/2 Associations (CIMBA): The authors would like to acknowledge the contribution of the staff of the genotyping unit under the supervision of Dr. Sylvie LaBoissière as well as Frédéric Robidoux from the McGill University and Genome Quebec Innovation Centre.

Breast Cancer Association Consortium (BCAC): We thank all the individuals who took part in these studies and all the researchers,
clinicians, technicians, and administrators who have enabled this work to be carried out.

Amsterdam Breast Cancer Study (ABCs): We thank Annegien Broeks, Sten Cornelissen, Richard van Hien, Linde Braaf, Senno Verhoef, Laura van ’t Veer, Emiel Rutgers, Ellen van der Schoot, and Femke Atsma.

Bavarian Breast Cancer Cases and Controls (BBCG): We thank Lothar Haerlecher, Sonja Oesper, Silke Landrith, and Reiner Strick. 

British Breast Study (BBS): We thank Eileen Williams, Elaine Ryder-Mills, and Kara Sargus.

Breast Cancer Family Registry (BCFR) Studies: Samples from the NC-BCFR were processed and distributed by the Coriell Institute for Medical Research. We wish to thank members and participants in the Breast Cancer Family Registry for their contributions to the study. The ABCFS would like to also thank Maggie Angelakos, Judi Maskill, and Gillian Dite. 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 U.S. Government or the BCFR.


Breast Cancer in Galway Genetic Study (BIGGS): We thank Niall McInerney, Gabrielle Colleran, Andrew Rowan, and Angela Jones.

BRCA-gene mutations and breast cancer in South African women (BMBSA): We wish to thank the families who contribute to the BMBSA study.

Beckman Research Institute of the City of Hope (BRICOH): We thank Greg Wilhoite, Yuan Chun Ding, Linda Steele, and Elaine Ryder-Mills for their work in participant enrollment and biospecimen and data management.

Breast Cancer Study of the University Clinic Heidelberg (BSUCH): We thank Peter Bugert, Medical Faculty Mannheim.

Copenhagen General Population Study (CGPS): We appreciate the staff and participants of the Copenhagen General Population Study. For the excellent technical assistance, we thank Dorteck Uhlen, Anette Olsen, Maria Birna Arnadottir, Anne Bank, and Dorthe Kjeldgaard Hansen.

Spanish National Cancer Centre (CNIO): We thank Alicia Barroso, Rosario Alonso, and Guillermo Pita for their assistance.

Spanish National Cancer Centre Breast Cancer Study (CNIO-BCS): We thank Charo Alonso, Guillermo Pita, Nuria Alvarez, Daniel Herrero, Primitiva Menendez, Jose Ignacio Arias Perez, Pilar Zamora, the Human Genotyping-CEGEN Unit (CNIO); for their help in the project. We also thank the technical and administrative staff in the laboratory.

European BRCA1 & BRCA2 Mutation Carriers (EBC1 & EBC2): Additional cases were recruited in the context of the VERDI study. We thank Hartwig Ziegler, Douglas F. Easton is the PI of the study. EMBRACE Coordinating Centres are: Copenhagen, M. Jørgensen, T. Classen; Edinburgh, J. Bremner, M. A. Reid; Genen Omgeving studie van de werkgroep Hereditair Genetisch ONderzoek (GEMO), Amsterdam, NL: J.J.P. Gille, Q. Waisfisz, H.E.J. Meijers-Heijboer, University Hospital Maastricht, NL: E.B. Gomez-Garcia, M.J. Blok; University Medical Center Groningen, NL: J.C. Oosterwijk, A.H. van der Hout, M.J. Mourits, G.H. de Bock. The Netherlands Foundation for the detection of hereditary tumours, Leiden, NL: H.F. Vasen.

Epidemiological study of BRCA1 & BRCA2 mutation carriers (EMBRACE): Douglas F. Easton is the PI of the study. EMBRACE Coordinating Centres are: Copenhagen, M. Jørgensen, T. Classen; Edinburgh, J. Bremner, M. A. Reid; Genen Omgeving studie van de werkgroep Hereditair Genetisch ONderzoek (GEMO), Amsterdam, NL: J.J.P. Gille, Q. Waisfisz, H.E.J. Meijers-Heijboer, University Hospital Maastricht, NL: E.B. Gomez-Garcia, M.J. Blok; University Medical Center Groningen, NL: J.C. Oosterwijk, A.H. van der Hout, M.J. Mourits, G.H. de Bock. The Netherlands Foundation for the detection of hereditary tumours, Leiden, NL: H.F. Vasen.

Gene Environment Interaction and Breast Cancer in Germany (GENICA): The GENICA network: Dr. Margarete Fischer-Bosch-Institute of Clinical Pharmacology, Stuttgart, and University of Tübingen, Germany; [C], Hiltrud Brauch), Department of Internal Medicine, Evangelische Krankenhaus Bonn, Bonn, Germany; [Yon-Duchows, Ko, Christian]; Institute of Pathology, University of Bonn, Bonn, Germany [Hand-Peter Fischer], Molecular Genetics of Breast Cancer, Deutsches Krebsforschungszentrum (DKFZ), Heidelberg, Germany [UH]; and Institute for Prevention and Occupational Medicine of the German Social Accident Insurance (lPA), Bochum, Germany [Thomas Breening, Beate Pesch, Sylvia Rabstein, Anne Spichenkova, VH].

Hospital Clinico San Carlos (HCSC): We acknowledge Alicia Tosar for her technical assistance.

Helsinki Breast Cancer Study (HEBCS): HEBCS would like to thank Drs. Kristiina Aittomäki, Clark Blomqvist and Kirsimari Aaltonen, and Taru A. Muranen and RN Irja Erkkilä for their help with the HEBCS data and samples.

Hannover-Minsk Breast Cancer Study (HMBCS): We thank Natalia Bogdanova, Natalia Antonenkova, Hans Christiansen, and Peter Hillerman.

Study of Genetic Mutations in Breast and Ovarian Cancer patients in Hong Kong and Asia (HRBCP): We wish to thank Hong Kong Sanatorium and Hospital for their continual support.

Molecular Genetic Studies of Breast- and Ovarian Cancer in Hungary (HUNBOCS): We wish to thank the Hungarian Breast and Ovarian Cancer Study Group members [János Papp, Aniko Bozsik, Kristof Arvai, Judit Franko, Maria Balogh, Gabriella Varga, Judit Ferenczi, Department of Molecular Genetics, National Institute of Oncology, Budapest, Hungary), and the clinicians and patients for their contributions to this study.

University Hospital Vall d’Hebron (HV1): We thank the study staff and participants.

Interdisciplinary HEalth Research Internal Team BReast Cancer Susceptibility (INHERIT): We would like to thank Dr. Martine Dumontie, Martine Tranchant for sample management and skillful technical assistance.

Kuopio Breast Cancer Project (KBCP): We thank Eija Myohanen and Helena Kemilainen.

Kathleen Cunningham Consortium for Research into Familial Breast Cancer (kConFab/AOCS): We 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 for their contributions to this resource, and the many families who contribute to kConFab.

Leuven Multidisciplinary Breast Centre (LMBC): We thank Gillian Peuteman, Dominiek Smets, Thomas Van Brussel, and Kathleen Corthouts.

Mammary Carcinoma Risk Factor Investigation (MARI): We thank Dieter Flesch-Janys, Rebecca Hein, Stefan Nickels, Muhallet Gelis, Sabine Behrens, and Ursula Eilber.

Milan Breast Cancer Study Group (MBCSG): We thank Daniela Zaffaroni of the Fondazione Istituto Nazionale Tumori, Milan, Italy and the personnel of the CGT laboratory at IFOM-IEO Campus, Milan, Italy.


National Israeli Cancer Control Center (NICCC): We wish to thank the NICCC National Familial Cancer Consultation Service team led by Sara Dishon, the lab team led by Dr. Flavio Lejbkowicz, and the research field operations team led by Dr. Milla Pinchev.

Oulu Breast Cancer Study (OBCS): We thank Katri Pylkas, Arja Jukkola-Vuorinen, Mervi Grip, Saima Kauppinen, Meri Otsukka, and Kari Mononen.

Ontario Cancer Genetics Network (OCGN): We thank the study staff and participants.

University Medical Centre Breast Cancer Study (ORIGO): We thank E. Krol-Warmerdam, and J. Blom for patient accrual, administering questionnaires, and managing clinical information. The LUMC survival data were retrieved from the Leiden hospital-based cancer registry system (ONCODC) with the help of Dr. J. Moolenaar.

The Ohio State University Comprehensive Cancer Center (OSUCCG): Kevin Sweet, Caroline Craven, and Michelle O’Connor were instrumental in accrual of study participants, ascertainment of medical records and database management. Samples were processed by the OSU Human Genetics Sample Bank.

Odense University Hospital (OUH): We thank the study staff and participants.

Università di Pisa (PBSG): We thank the study staff and participants.

The U.S. National Cancer Institute Polish Breast Cancer Study (PBCS): We thank the study collaborators Drs. Louise Brinton, Mark Sherman, Stephen Chanoock, Neolina Szeszenia-Dabrowska, Beata Peplonska, and Witold Zatonski, as well as Pei Chao and Michael Stagner, for their data management support.

Rotterdam Breast Cancer Study (RBSC): We thank Petra Bos, Janmet Blom, Ellen Crepin, Elisabeth Huijskens, Annette Heemskerk, and the Erasmus MC Family Cancer Clinic.

Sheffield Breast Cancer Study (SBCS): We thank Sue Higham, Helen Cripps, and Dan Comber.

South East Asian Breast Cancer Association Study (SEABASS): 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 MyBeCa Study for assistance in patient recruitment, data collection, and sample preparation. In addition, we thank Philip Iu, Sng Jen-Hwei, and Sharifah Nor Akmal for contributing samples to the Singapore Breast Cancer Study and the HUKM-HKL Study respectively.

Study of Epidemiology and Risk Factors in Cancer Heredity (SEARCH): We thank the SEARCH and EPIC teams.

Sheba Medical Centre (SMC): SMC team wishes to acknowledge the assistance of the Meirav Comprehensive breast cancer center team at the Sheba Medical Centre for assistance in this study.

Swedish Breast Cancer Consortium (SWE-BCRA): Swedish scientists participating as SWE-BCRA collaborators are: from Lund University and University Hospital: Åke Borg, Håkan Olsson, Helena Jernström, Karin Henriksson, Katja Harbst, Maria Soller, Niklas Loman, Ulf Kristoftersson; from Gothenburg Sahlgrenska University Hospital: Anna Olsvikom, Margareta Nordling, Per Karlsson, Zakaria Einbeigi; from Linköping University Hospital: Johan Rosén, Roland Jonsson, and Taru A. Muranen and RN Irja Erkkilä for their help with the HEBCS data and samples.

The U.S. National Cancer Institute Polish Breast Cancer Study (PBCS): We thank the study collaborators Drs. Louise Brinton, Mark Sherman, Stephen Chanoock, Neolina Szeszenia-Dabrowska, Beata Peplonska, and Witold Zatonski, as well as Pei Chao and Michael Stagner, for their data management support.

Rutgers Breast Cancer Study (RBSC): We thank Petra Bos, Janmet Blom, Ellen Crepin, Elisabeth Huijskens, Annette Heemskerk, and the Erasmus MC Family Cancer Clinic.

University Hospital Vall d’Hebron (HV1): We thank the study staff and participants.

Interdisciplinary HEalth Research Internal Team BReast Cancer Susceptibility (INHERIT): We would like to thank Dr. Martine Dumontie, Martine Tranchant for sample management and skillful technical assistance.

Kuopio Breast Cancer Project (KBCP): We thank Eija Myohanen and Helena Kemilainen.

Kathleen Cunningham Consortium for Research into Familial Breast Cancer (kConFab/AOCS): We 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 for their contributions to this resource, and the many families who contribute to kConFab.

Leuven Multidisciplinary Breast Centre (LMBC): We thank Gillian Peuteman, Dominiek Smets, Thomas Van Brussel, and Kathleen Corthouts.
Cecilia Zvorec, 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.

University of California Los Angeles (UCLA): We thank Joyce Seldon MSGC and Lorna Kwan MPH for assembling the data for this study.

University of California San Francisco (UCSF): We would like to thank Ms. Salina Chan for her data management and the following genetic counselors for participant recruitment: Beth Crawford, Nicola Stewart, Julie Mak, and Kate Lamvik.

Royalty Breakthrough Generation Study (UKBGS): We thank Simon Gayther, Susan Ramus, Carole Pye, Patricia Seldon MSGC and Lorna Kwan MPH for assembling the data for this study.

United Kingdom Familial Ovarian Cancer Registries (UKFOCR): We thank Simon Gayther, Susan Ramus, Carole Pye, Patricia Harrington, and Eva Wozniak for their contributions towards the UKFOCR.

Vicrctorian Familial Cancer Trials Group (VFCTG): We acknowledge Geoffrey Lindeman, Marion Harris, Martin Delataycy of the Victorian Familial Cancer Trials Group. We thank Sarah Sawyer and Rebecca Driesen for assembling this data and Ella Thompson for performing all DNA amplification.

Author Contributions


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