

Hereditary Breast Cancer

BRCA1 and BRCA2 are the most well-known genes linked to breast cancer risk. Together, the two genes are thought to explain a large portion of hereditary breast and ovarian cancers.

For this reason, Susan G. Komen for the Cure[®] has dedicated more than \$24 million of its \$550 million research portfolio to BRCA1/2 research starting with a grant in 1993 to Dr. Mary-Claire King. At the time, Dr. King had identified an area on Chromosome 17 that was linked to familial breast cancer, but had not found the gene itself. This Komen grant supported the identification (sequencing) of the BRCA1 gene. Since then, Komen for the Cure has funded 82 grants looking at mutations in the BRCA1/2 genes, including awards to Dr. King in 1994 and 1996 to further characterize BRCA1 and its role in familial breast cancer.

Understanding BRCA1 and BRCA2 Mutations and Breast Cancer

BRCA1 and BRCA2 are critical for repairing mistakes in DNA, which are commonly introduced in dividing cells. In women with BRCA1 or BRCA2 mutations, some cells cannot fix one type of DNA error, leading to the accumulation of mistakes in the DNA and, in some cases, breast cancer. Current Komen-funded research is looking at:

- BRCA1/2 mutations in specific populations—such as Bahamians, African-Americans, Latinas—to determine if specific mutations are associated with ancestry and/or more aggressive forms of the disease
- The role of BRCA1/2 in the repair of DNA and chromosome stability to better understand how BRCA1/2 mutations lead to breast cancer and to identify targets for new drugs
- Additional specific mutations (called SNPs) that can be used to develop low-cost screening tools

- Interactions between BRCA1/2 and environmental and/or hormonal factors so that steps can be taken to manage the risk of developing breast cancer
- The role of BRCA1/2 in ductal carcinoma in situ (DCIS): does it predict more aggressive forms of DCIS?
- Other genes and proteins that interact with BRCA1/2 and may contribute to breast cancer

Preventing breast cancer in BRCA1 and BRCA2 mutation carriers

BRCA1/2 mutations can be passed to you through your mother's or your father's side of the family and can affect the risk of both female and male cancers. Women who carry a BRCA1 or BRCA2 genetic mutation have a much higher risk of breast cancer. Not all BRCA1/2 carriers, however, will get breast cancer; up to 40 percent of women with a BRCA1 mutation will never have breast cancer. It is likely that a combination of factors, such as lifestyle, determines who will get breast cancer.



One of Komen's Promise Grants, totaling almost \$5 million, is studying ways to potentially prevent breast cancer in BRCA1/2 mutation carriers. Dr. Judy Garber and her colleagues at the Dana-

Farber Cancer Institute are studying a new class of drugs, called PARP inhibitors, as potential chemoprevention for individuals with BRCA mutations. Tumor cells in individuals with BRCA1 or BRCA2 mutations are already hampered in their ability to repair damaged DNA. PARP inhibitors block the activity of Poly ADP Ribose Polymerase (or PARP), an enzyme involved in a back-up DNA repair pathway, causing the tumor cells to accumulate so many mistakes in the DNA that they must self-destruct. The hope is that PARP inhibitors will be a safe and effective way to reduce breast cancer risk or delay breast cancer in high-risk individuals with BRCA1/2 mutations.

**Active BRCA 1 & 2 Research Grants by Award Year
(as of February 2011)**

- 2010** Judy Garber Dana-Farber Cancer Institute
Preclinical and Brief Exposure Early Clinical Evaluation Of An Oral PARP Inhibitor For Breast Cancer Prevention In BRCA Mutation Carriers (Promise Grant)
- Lucia Guidugli, Fellow
Fergus Couch, Mentor Mayo Clinic and Foundation
Characterization of BRCA2 variants of uncertain significance (VUS) using genetic and functional approaches (Post Doctoral Fellowship - Translational Research)
- 2009** Stephanie Dance, Fellow
Chuck Perou, Mentor University of North Carolina at Chapel Hill
Molecular Characterization Of Breast Tumors Subtypes In An Effort To Tailor Specific Cancer Therapies (Post Doctoral Fellowship - Translational Research)
- Judith Hurley University of Miami School of Medicine
Evaluation of Genetic Risk In Bahamian Women With Breast And Ovarian Cancer (Special Award)
- 2008** Elizabeth Alli, Fellow
James Ford, Mentor Stanford University
BRCA1-mediated Regulation of Oxidative DNA Damage in Breast Cancer (Post Doctoral Fellowship - Basic Research)
- Fergus Couch Mayo Clinic and Foundation
Genetic risk factors for BRCA1 deficient and basal breast cancer (Investigator Initiated Research)
- Niu Hengyao, Fellow
Patrick Sung, Mentor Yale University
Role of the Tumor Suppressors BRCA2 and PALB2 in Chromosome Damage Repair (Post Doctoral Fellowship - Basic Research)
- Giovanni Parmigiani Dana-Farber Cancer Institute
Improvement and Validation of BRCAPRO (Investigator Initiated Research)
- Simon Powell Memorial Sloan-Kettering Cancer Center
Targeting DNA Repair Deficiencies in Human Breast Cancer (Investigator Initiated Research)
- Yue Xiong University of North Carolina at Chapel Hill
Controlling Mammary Luminal and Basal Progenitor Cell Proliferation, Differentiation, and Tumorigenesis (Investigator Initiated Research)
- 2007** Insoo Bae Georgetown University
Role of BRCA1 in Environmental Stress (Focused Areas of Study - Environmental Research Methods)
- Simonne Longerich, Fellow
Eloise Dray, Mentor Yale University
Molecular Basis of BRCA2-mediated Repair of Chromosome Damage (Post Doctoral Fellowship)
- Robert V. Skibbens Lehigh University
Cohesion-dependent Mechanisms of Cancer Progression And Aneuploidy (Basic, Clinical and Translational Research Grant)
- Donato Romagnolo University of Arizona at Tucson
Epigenetic Silencing of BRCA-1 and Protective Effects of Dietary Components (Basic, Clinical and Translational Research Grant)
- Qin Yang Washington University in St. Louis
BRCA1 Regulates AKT1 Activity in Breast Cancer (Basic, Clinical and Translational Research Grant)