Susan G. Komen
Research Grants – Fiscal Year 2014

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Identification of new genes for inherited breast cancer by application of next generation sequencing in high-risk families

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Lead Organization: University of Washington
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Public Abstract:
The discoveries of BRCA1 and BRCA2 changed breast cancer prevention and treatment in remarkable ways. It is now possible for women to learn if they carry cancer-predisposing mutations in BRCA1 and BRCA2, and if so, to take steps to prevent breast and ovarian cancer. One of our greatest frustrations is to discover that a family severely affected with breast cancer carries no detected mutation in any gene. In our studies of extended families at high risk of breast cancer, we have confronted this frustration many times. Our analyses of >800 severely affected families suggest that many mutations and genes for breast cancer predisposition remain to be found. Indeed, most severely affected families remain unresolved.
There are at least 18 genes with mutations responsible for inherited breast cancer. BRCA1 and BRCA2 are the best known, conferring extremely high risks of breast and ovarian cancer. Inherited mutations in TP53, CDH1, PTEN, STK11 are associated with very high risks of breast cancer in the contexts of rare syndromes. Inherited mutations in several genes in pathways critical to genomic integrity confer 2- to 4-fold increased risks of breast cancer; that is lifetime risks of 20% to 50%. These genes include Abraxas, ATM, BARD1, BRIP1, CHEK2, PALB2, RAD51C, RAD51D, ATR, BAP1, CHEK1, and GEN1. Recommendations for care of women with mutations in these more recently characterized genes include increased surveillance, including tools such as MRI that are not offered universally. In this Komen project, we will screen for novel mutations in the non-coding regions of breast cancer genes. Such mutations regulate the time and tissues of gene expression. The integration of high throughput genomics with information on regulatory elements with the genetic material and clinical information provided by our participating families provides an ideal opportunity to identify novel mutations and new mechanisms for inherited breast cancer. We will identify regulatory mutations specifically from families severely affected with breast cancer. If successful, our results will allow preventive management strategies to be extended to many families for whom the genetic cause of breast cancer is currently unknown. This proposal has the potential to improve patient care in the next few years by yielding a more comprehensive genomic profile of breast cancer predisposition. The short-term goals are to better identify women at risk, and to allow closer surveillance The long term goals are to contribute to the design of new prevention strategies and a better understanding of the mechanisms involved in breast cancer development.