Susan G. Komen for the Cure
Research Grants – Fiscal Year 2011

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Identifying the Missing Heritability of Breast Cancer.

Investigator(s): Melissa Southey, PhD
University of Melbourne,
Grant Mechanism: Post Doctoral Fellowship - Basic Research

Fellow: Tu Nguyen-Dumont, PhD
Awarded: $180,000.00
Research Focus: Biology

Public Abstract:
Hypothesis and how it will be tested: A proportion of breast cancer occurs in family clusters with many members of families being affected in several generations often at young ages. Some of the genetic factors responsible for these multiple-case breast cancer families have been identified and some women and their families can receive genetic counselling and clinical management specifically addressing the mutation that is known to be segregating in their families. However, all the known breast cancer predisposition genes combined only account for approximately 30-35% of the familial risk, leaving two thirds unexplained. Identifying the genes and associated mutations responsible for the large unexplained proportion of familial breast cancer is fundamental to improving the clinical care and importantly the risk management of the significant proportion of women and their multiple-case breast cancer families who test negative for mutations in the known breast cancer susceptibility genes (eg BRCA1 and BRCA2). Management of these women is currently challenging and genetic counselling is limited to using risk estimates based on their family history which even when accurately reported, well collected and verified is often uninformative, unless extreme. Traditional linkage analysis in highly selected multiple-case breast cancer families has not proven fruitful since the discovery of BRCA1 and BRCA2, leading to the hypothesis that no single gene is likely to account for a large fraction of the remaining familial clustering of breast cancer. Alternative strategies for identifying the remaining genes that when mutated contribute to breast cancer susceptibility are now available. This methodology can systematically sequence the entire human exome (all the coding region of the genome). This methodology applied to the exomes of multiple-case breast cancer families, combined with new analytical pipelines capable of identify rare genetic variants in putative breast cancer susceptibility genes now offers a new and powerful approach to identifying the majority of the yet unidentified breast cancer susceptibility genes. Hypothesis: The majority of the yet unidentified breast cancer susceptibility genes can be identified using whole-exome massively parallel sequencing applied to highly selected breast cancer families from international resources. The proportion of breast cancer that these genes are responsible for can be estimated by further mutation screening in a larger series of affected young women from multiple-case breast cancer families. Uniquely advances our understanding of breast cancer leading to reduction in incidence and or mortality: Identification of novel breast cancer predisposition genes with proven mutations in multiple-case breast cancer families will be of immense interest and assistance for those families and will expand our biological understanding of breast cancer predisposition and development. Testing these genes in a larger set of DNAs from young affected women from families with less dramatic family histories of breast cancer will more accurately characterise what proportion of familial breast cancer each gene explains, the associated risks and

possible associated phenotypes. This work will provide the evidence base from which clinical cancer genetics can adopt mutation screening of a larger number of susceptibility genes for breast cancer. Identification of the majority of the remaining unidentified breast cancer predisposition genes will mean that the majority of women at high genetic risk of breast cancer will be identifiable, at a stage when many of them are still unaffected and can be offered appropriate clinical management for their known risks. This work will significantly progress individualised medicine in the field of breast cancer in areas such as breast cancer prevention, risk estimation, early detection, screening recommendations, treatment selection (genotype specific/targeted therapies) and improved prognosis leading rapidly to reductions in incidence and mortality. Importance of research to patients with breast cancer: This work will enable the identification of a gene mutation, for the majority of women with breast cancer that has been caused by a genetic factor to be identified in a breast cancer predisposition gene. This will include women with a family history of breast cancer and women diagnosed at a young age. Knowing a woman's gene mutation status (especially if known at the time of diagnosis) will increasingly assist good treatment choices, educate surgical options and instruct cancer prevention strategies. Once the family mutation has been identified this new genetic information can be used to identify other family members who are at significantly elevated risk for breast cancer, many of whom before they are affected and who will benefit most from improved screening and other breast cancer preventive strategies. This new genetic information can also be used to identify members of the patient's families who are at population risk (non-mutation carriers) who can be relieved of further intensive screening.

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