Report NCU grant

Report submission date: May 28st 2013

Main applicant: Rosa B. Barkardottir

Project title: Molecular Epidemiology of Familial Breast Cancer in the Nordic Countries. Search for Novel Genes in High-Risk Families

NCU grant received (€): 130.000 (60.000 in 2012 and 70.000 in 2013)

Project commencement and completion dates: January 2012 - ongoing

Please e-mail report to: ncu@kreftforeningen.no

---

1. Brief description of the project, written in a language understandable to non-scientists (Maximum length: 100 words)

In this NCU project we study high-risk breast cancer (BC) families not explained by BRCA1 and BRCA2. The aim is to identify novel BC genes and to better understand the inheritance of BC susceptibility and the molecular contribution to BC. Increased knowledge could be utilised in genetic counselling and predictive testing could result in earlier diagnosis and better follow-up of individuals who are at an increased risk. Also, identification of new BC genes opens up the possibility for new avenues of research, resulting in better understanding of the biology of BC and leading to improvements in diagnostics and specialized treatment.

2. Summarize the major findings of the project (Maximum length: 400 words)

In May 2013, whole genome or exome sequencing have been performed on a total of 50 DNA samples from 17 high-risk non-BRCA1/2 families (26 samples from 7 Icelandic families and 24 samples from 10 Finnish families). The sequencing data is enormous and a huge effort has been used to establish effective pipelines to clean the data to minimise the number of false positive mutations. This has been successful for the whole exome sequencing data and we are planing a collaboration with bioinformatics company in USA cleaning further the whole genomic sequencing data. Currently, we are verifying/evaluating suggestive causative mutations and variants detected in the whole exome sequence data. Until now we have detected several suggestive mutations and variants in known BC susceptibility genes. Founder mutations were indentified in RAD51C and RAD51D genes in the Finnish breast cancer families and screened in other ancer types as well (see publication list below). We also have a long list of suggestive variants, as well as mutations, in genes that have not previously been implicated in hereditary BC. These need to be verified and evaluated further.

In Sweden a national prospective research study (SWEA) started in 2012 with the aim to investigate the contribution of mutations in a larger set (>60) of possible susceptibility genes in familial breast cancer, in parallel to the clinical testing for BRCA1 and BRCA2. Finland joined the study in 2013. Until know ~600 families have been analysed. The frequency of BRCA1 and BRCA2 mutations are 8% and 4% respectively. TP53 mutations are found in 1-2% of families but

deleterious mutations in PTEN, STK11, CDH1 are very rare, as expected, but appear in unexpected families. CHEK2 mutations (or functionally defect variants) are present in 7% of families, all BRCA1/2 negative. Truncation and splice site mutations in PALB2, BARD1, BRIP1, RAD51C and other known BRCA1/BRCA2 associated genes, also contribute to increase the proportion of families with mutation in any susceptibility gene. Loss-of-function variants are also found in other genes of the BRCA/Fanconi anemia pathway that has not previously been implicated in breast cancer predisposition. Some families (index cases) carry more than one of these variants, with or without concomitant BRCA mutation. Segregation analysis will be used to further investigate the possible contribution of all these variants, as will screening of larger materials of (anonymized) healthy individuals and unselected breast cancer cases to determine their population frequency.

Our preliminary data suggest that many novel BC susceptibility genes are still to be found but each of them will only account for a very small fraction of BC families. The moderate penetrance mutations also may have joint risk effects. Examining a larger number of BC families is needed to yield a more comprehensive understanding of familial BC predisposition.

3. Describe how the project has increased our knowledge of the prevention, cause and/or cure for cancer (Maximum length: 150 words)

Molecular epidemiology spectra of already known BC genes and variants are being successfully evaluated in the Nordic countries, BRCA1 and BRCA2 and modyfing genes being the best examples. However, the genetic background of BC is still largely unknown and new BC genes and variants need to be identified. The likelihood of detecting new ones will increase by searching for them in well characterised high-risk BC families, with the option of a follow up in a large population-based patient materials. Our NCU project is in its early face (second year) and it is anticipated that it will increase our understanding of BC susceptibility and result in identification of new susceptibility genes and variants. The prospective nature of the study facilitates dissemination and clinical use of relevant results in counselling, follow-up and disease prevention.

4. Outline how Nordic cooperation has added value to this project (Maximum length 100 words)

The synergistic effect of our study lies in pooling sequencing data from high-risk Nordic families thus increasing the likelihood of success in identifying new BC genes and in increased understanding of molecular contribution to BC. The synergistic effect lies as well in the follow-up studies of identified BC genes, by pooling our large population-based sets of BC families, unselected BC patients and controls. Furthermore, it lies in our extensive clinical-pathological data linked to the BC cases; our global mRNA and miRNA gene expression and array-CGH data already generated from up to 600 Nordic BC tumours; and our tumour tissue arrays produced for more than 1500 breast tumours.

5. Publications resulting from this grant

Pelttari LM, Kiiski J, Nurminen R, Kallioniemi A, Schleutker J, Gylfe A, Aaltonen L, Leminen A, Heikkilä P, Blomqvist C, Bützow R, Aittomäki K, Nevanlinna H. A Finnish founder mutation in *RAD51D*: analysis in breast, ovarian, prostate and colorectal cancer. J Med Genet 49: 439-432, 2012

Pelttari LM, Nurminen R, Gylfe A, Aaltonen LA, Schleutker J, Nevanlinna H. Screening of Finnish *RAD51C* Founder Mutations in Prostate and Colorectal Cancer Patients. BMC Cancer 12:552, 2012