NCU – Summative report for 2013

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

NCU grant received (€): 70.000 euros

Project commencement date: 2012.1.1
Completion date: 2014.12.31

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1. Briefly describe the project in a language understandable to non-scientists (max. 100 words)

The genetic background of breast cancer is still largely unknown and the objective of this Nordic Cancer Union project is to identify new breast cancer susceptibility genes or variants to better understand the molecular contribution to breast cancer. We used next generation sequencing data from members of high-risk non-BRCA1/2 families in which we detected a number of mutations in suggestive novel genes that are being validated. Identification of additional susceptibility genes is essential for further development of predictive testing. It would also open up the possibility for new avenues of research, resulting in better understanding of the biology of breast cancer that will lead to improvements in diagnostics and specialized treatment.

2. Summarize the major findings of the project (max. 400 words)

Through this current Nordic collaboration project the Finnish and the Icelandic groups have performed whole genome or exome sequencing (WGS and WES) 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 11 Finnish families). The majority of the families included in our whole genome or exome sequencing project are high-risk families with suggestive dominant inheritance of breast cancer susceptibility. We therefore expected that in the majority of the families the main causal factors would include mutations with moderate to high penetrance.

In this first round of analysis of our WES and WGS data the main emphases have been on mutations in the protein coding regions of the genes, predicted to have a pathogenic effect. We detected several new suggestive mutations and variants in already known breast cancer susceptibility genes. Founder mutations were indentified in RAD51C and RAD51D genes in the Finnish breast cancer families and have been screened in other cancer types as well. The WGS and WES results also include a large number of suggestive mutations and

variants in genes that have not been implicated in breast cancer previously. The most interesting ones (based on functional annotations of the genes) were prioritized for large scale validation analyses in breast cancer cases and population controls. Preliminary results suggest a significant, moderate breast cancer risk for a protein truncating mutation in a putative novel breast cancer susceptibility gene. A large number of suggestive low to moderate penetrant mutations still awaits verification and further evaluation.

The approach of the Swedish group is different from the Finnish and the Icelandic groups. In Sweden, the SWE-BRCA Extended Analysis study has been running since April 2012, in parallel to the clinical BRCA-screening routines. Massively parallel sequencing of SureSelect captured DNA (whole genomic region or coding regions of 65 selected genes) is performed and followed by Sanger sequencing confirmation of relevant mutations and variants. Findings in clinically established high-risk breast cancer genes (BRCA1, BRCA2, TP53, PTEN, LKB1, CDH1) and in CHEK2 (moderate-risk) are reported back for counselling, whereas results from other candidate breast cancer susceptibility genes (of the BRCA/Fanconi anemia signalling pathway) are further investigated by segregation and association analysis. So far >800 index cases have been recruited from Swedish and Finnish breast cancer families and the results show that less than 40% of these cases are explained by previously known breast cancer susceptibility genes.

In short, from our preliminary Nordic data it is becoming increasingly clear that the complexity of molecular epidemiology of familial breast cancer in the Nordic countries is high and examining a larger number of families will be needed to yield a more comprehensive understanding of familial predisposition.

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

Our study is still ongoing and we have identified several new suggestive mutations and variants in both known and unknown but suggestive breast cancer susceptibility genes. When validated some of these findings will be useful in predictive testing and some will also open up the possibility for new avenues of research. Our data also suggest that many novel breast cancer susceptibility genes and variants are still to be found in the Nordic breast cancer material and that the genetic complexity within high risk families is high.

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

Added value of this Nordic collaboration is pooling of research material and research data as well as sharing valuable experience in a highly challenging and cutting edge research environment. Furthermore, the synergistic effect of our study lies not the least in the potential follow-up studies of identified BC genes, by pooling our large population-based sets of BC families, unselected BC patients and unselected controls; 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.