NCU – Summative report for 2014

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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 (€): 80.000

Project commencement and completion dates: ***01.01.2012 - 31.12.2014***

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

The objective of the project was to identify new breast cancer susceptibility genes and variants. The search was based on next generation sequencing data from members of Icelandic and Finnish high-risk non-BRCA1/2 families. We also continued looking for new variants within selected BC candidate genes including both prospective screening in families and cases/controls analysis using a 64-gene panel of known and potential breast cancer susceptibility genes. Identification of additional susceptibility genes and variants is essential for further development of predictive testing and it opens new avenues of research that could lead to improvements in diagnostics and specialized treatment.

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

Whole genome or exome sequencing was performed on 50 DNA samples from 17 high-risk non-BRCA1/2 families. The sequencing data is enormous and analysing it is a huge challenge. In this NCU project the main emphasis was on potential mutations in protein coding regions and splice site domains. The most interesting ones were prioritized for large-scale validation analyses in BC cases and controls. It resulted in the identification of moderate risk variants in two new BC genes. One is a nonsense mutation within the FANCM, which is known to be involved in the Fanconi anemia signalling pathway. The mutation (c.5101C>T) was found to associate with BC risk in Finland but was not detected in Iceland. It is also seen in the Swedish population and cases/control analyses is ongoing. Interestingly, the highest mutation frequency was observed among triple-negative BC patients, further implicating DNA repair in the etiology of this aggressive form of BC. The other variant was identified within a gene located in the endoplasmic reticulum. Clinically based analysis showed that the expression of this gene

correlates with parameters that suggest poor prognosis and shorter survival in ER positive luminal breast tumors.

Screening of selected candidate genes resulted in several new BC variants in already known susceptibility genes, including founder mutations in RAD51C and RAD51D in Finnish families. The SWE-BRCA extended analysis study led by Ake Borg has also revealed new variants within genes of the BRCA/Fanconi anemia signalling pathway, all very rare. More than 2000 prospective familial cases have been analysed using massively parallel sequencing of 64 selected candidate genes. Included are clinically established high-risk (BRCA1, BRCA2, TP53, PTEN, LKB1, CDH1, PALB2) and moderate-risk (e.g. RAD51C/D, CHEK2) BC genes and the results for them are reported to clinicians for counselling and/or further segregation analysis. Based on the current data, BRCA1 and BRCA2 mutations occur in around 12% of familial cases in Sweden but mutations in other clinically established risk genes are rare and combined found in approximately 1% of the cases. In Sweden, screening of geographically matched populations of 5000 controls, 5000 unselected BC cases and 2000 retrospective familial cases, using the same 64-gene panel, is used to distinguish risk variants from neutral variants.

It is clear that the complexity of the molecular epidemiology of familial BC in the Nordic countries is high and examining larger numbers 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)

The objective of the project was to identify new breast cancer susceptibility genes and variants; this was achieved as well as showing potential clinical relevance in breast cancer of two newly identified genes. The project thus added to our knowledge of genes and variants that increase the risk of breast cancer, that can be helpful for further development of predictive testing, and that open up the possibility of research which eventually could lead to improvements in diagnostics and specialized treatment. Furthermore, through the SWE-BRCA project a new knowledge regarding truncating germline mutations in CHEK2 (such as c.1100delC) indicate that these mutations may be of importance for treatment of affected carriers because of the significant risk of contralateral disease.

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. The synergistic effect of our study lies 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 for up to 600 Nordic BC tumours; and our tumour tissue arrays produced for more than 1500 breast tumours.

5. Publications resulting from the NCU research 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

Kiiski JI, Pelttari LM, Khan S, Freysteinsdottir ES, Reynisdottir I, Hart SN, Shimelis H, Vilske S, Kallioniemi A, Schleutker J, Leminen A, Bützow R, Blomqvist C, Barkardottir RB, Couch FJ, Aittomäki K, Nevanlinna H. Exome Sequencing identifies FANCM as a susceptibility gene for triple-negative breast cancer. Proc Natl Acad Sci U S A. 2014 Oct 21;111(42):15172-7. doi:

Reynisdottir I, Freysteinsdottir ES, Arason A, Agnarsson BA, Gudmundsdottir ET, Marzelliusardottir A, Kiiski J, Einarsson H, Johannesdottir G, Kristjansdottir S, Johannsson O, Borg A, Nevanlinna H, Amundadottir LT, Barkardottir RB. Whole genome sequencing identifies xxxx as a novel breast cancer gene: xxxx insG is a rare moderate risk variant but regardless of carrier status high xxxx transcript level correlates with worse prognosis for patients with estrogen receptor positive luminal tumors. Submitted

Ehrencrona H, Einbeigi Z, Paulsson-Karlsson Y, Kvist A, Lindblom A, Melin B, Stenmark Askmalm M, Törngren T, Arver B, Borg Å. The SWEA study - an extended analysis of hereditary breast cancer in Sweden. Abstract ESHG meeting 2014