Report NCU grant

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Main applicant: **Heli Nevanlinna and Per Hall**

Project title: **Molecular epidemiology of breast cancer risk and progression**

NCU grant received (€): **150 000 €**

Project commencement and completion dates: **1.3.2010-28.2.2011**

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

In the management of breast cancer, early detection or cancer prevention on one hand and development of individualized therapy on the other hand are of central importance. Despite the recent advances in understanding mechanisms behind breast cancer, the genetic risk factors for breast cancer development and especially for tumor progression and survival are still largely unknown, and no biomarkers are currently available in clinical use that would predict response to specific chemotherapeutic agents. In this project, we aimed to identify the inherited genetic variation for breast cancer risk or for progression and survival as well as therapy outcome.

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

We used complementary pathway-based and genome wide approaches to identify genetic variants for breast cancer risk or survival in Finnish and Swedish breast cancer patient series, in collaboration with Dr. Jianjun Liu (Genome Institute of Singapore). 156 p53/NFkB transcription factor binding site SNPs were genotyped and we found that a common SNP within an intronic p53 binding motif which interrupts the down-regulation of AMPK protein by p53 is associated with cancer susceptibility (Liu et al. 2010). Further analyses of other SNPs are still ongoing.

The estrogen metabolizing pathway has also been analyzed. We investigated 34 genes on the risk of breast cancer. Although none of the genes alone had a significant influence on the risk, the androgen converting sub-pathway was significantly associated to the risk of breast cancer (Low et al. 2010). Additionally, about 840 SNPs from estrogen receptor co-factors (co-regulators, co-activators, co-reperssors) have been genotyped in the Finnish and Swedish sample sets. Statistically significant global p-values were found for 70 genes in AML analysis. Most specifically, a significant interaction was found between genetic variants in ESR1 and its co-activator PPARGC1B in both study populations, with more than 2-fold increased risk for carriers (Li Y. et al. 2011).

Genome wide SNP analysis of breast cancer risk of Swedish and Finnish patients confirmed low penetrance breast cancer risk variants recently found also in other populations. Genome-wide pathway-analysis of all cases as well as the ER-negative subgroup indicated breast cancer risk association with SNPs in genes in specific pathways. These results suggest that further analysis of SNPs in these pathways may identify associations that would be difficult to detect through agnostic single SNP analyses. (Li J. et al 2010a, b).

Based on a genome-wide SNP analysis for breast cancer survival, we have identified several genomic regions where SNPs show significant main association with breast cancer survival or with survival in specific treatment or phenotypic subgroups. Large scale validation analyses are ongoing as international collaborative studies.

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

The results obtained from this project reveal new insights into the mechanisms and pathways for breast cancer development and add to the information basis for a longer term goal of identification of personal risk profiles for development of individualized diagnostics as well as prediction models for treatment decisions. This will have impact on reducing morbidity and mortality from breast cancer, with implications also on the outcome and cost-effectiveness of health care for cancer prevention or cancer treatment.

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

The Nordic co-operation has enabled studies based on the 1) large and well characterised sample and data sets of the collaborating groups 2) the high quality and uniform health care systems in Sweden and Finland with availability and reliability of clinical data 3) the high coverage of the National Tumor and Cancer Registries and 4) the extensive collaborative network for the high-throughput genetic and bioinformatic analyses as well as follow-up and validation studies. These together with the extensive data sets generated during the present funding period form a strong basis also for further collaborative studies.

5. Publications resulting from this grant

Liu J, Desai KV, Li Y, Banu S, Lee YK, Qu D, Heikkinen T, Aaltonen K, Muranen TA, Kajiji TS, Bonnard C, Aittomäki K, von Smitten K, Blomqvist C, Hopper JL, Southey MC, Brauch H; The GENICA Consortium, Chenevix-Trench G, Beesley J, Spurdle AB, Chen X; Kathleen Cuningham Foundation Consortium for Research into Familial Breast Cancer; Australian Ovarian Cancer Study Group, Czene K, Hall P, Nevanlinna H, Liu ET. Germ-line variation at a functional p53 binding site increases susceptibility to breast cancer development. Hugo J 3:31-40, 2010

Low YL, Li Y, Humphreys K, Thalamuthu A, Li Y, Darabi H, Wedrén S, Bonnard C, Czene K, Iles MM, Heikkinen T, Aittomäki K, Blomqvist C, Nevanlinna H, Hall P, Liu ET, Liu J. Multi-variant pathway association analysis reveals the importance of genetic determinants of estrogen metabolism in breast and endometrial cancer susceptibility. PLoS Genet. 6:e1001012, 2010

Li J, Humphreys K, Heikkinen T, Aittomäki K, Blomqvist C, Pharoah PD, Dunning AM, Ahmed S, Hooning MJ, Martens JW, van den Ouweland AM, Alfredsson L, Palotie A, Peltonen-Palotie L, Irwanto A, Low HQ, Teoh GH, Thalamuthu A, Easton DF, Nevanlinna H, Liu J, Czene K, Hall P. A combined analysis of genome-wide association studies in breast cancer. Breast Cancer Res Treat. 2010 Sep 26. [Epub ahead of print]

Li J, Humphreys K, Darabi H, Rosin G, Hannelius U, Heikkinen T, Aittomäki K, Blomqvist C, Pharoah PDP, Dunning AM, Ahmed S, Hooning MJ, Hollestelle A, Oldenburg RA, Alfredsson L, Palotie A, Peltonen-Palotie L, Irwanto A, , Low HQ, Teoh GHK, Thalamuthu A, Kere J, D'Amato M, Easton DF, Nevanlinna H, Liu JJ, Czene K, Hall P. A genome-wide association scan on ER-negative breast cancer. Breast Cancer Res 12:R93, 2010

Li Y, Li Y, Wedrén S, Li G, Charn TH, Desai KV, Bonnard C, Czene K, Humphreys K, Darabi H, Einarsdóttir K, Heikkinen T, Aittomäki K, Blomqvist C, Chia KS, Nevanlinna H, Hall P, Liu ET, Liu J. Genetic variation of ESR1 and its co-activator PPARGC1B is synergistic in augmenting the risk of estrogen receptor-positive breast cancer. Breast Cancer Res 13(1):R10, 2011