NCU – Summative report for 2014

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Project title: Search for novel high-penetrance susceptibility genes for familial colorectal cancer from Finnish and Danish cohorts

NCU grant received (€): 45 000

Project commencement and completion dates: Jan 1st, 2014 – Dec 31st, 2016

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

Up to one-third of colorectal cancers cluster in families and 5% are clearly hereditary. Lynch syndrome, which results from inherited mutations in DNA mismatch repair genes, is the most prevalent form of hereditary colorectal cancer. This project focuses on a new entity clearly distinct from Lynch syndrome and known as Familial Colorectal Cancer Type X (FCCX). We aim to investigate 100 FCCX families from the Finnish and Danish cohorts with the purpose to determine the prevalence of mutations in two susceptibility genes we have discovered previously and to identify novel predisposing genes in the major fraction of FCCX families that are mutation-negative at present. Our research increases the understanding of colorectal tumorigenesis and offers new tools for targeted cancer prevention in high-risk families.

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

A comprehensive investigation of a four generation FCCX family from Finland resulted in the discovery of RPS20 as a novel colon cancer susceptibility gene (**Nieminen et al., Gastroenterology 147: 595-598, 2014**). RPS20 encodes a component (S20) of the small ribosomal subunit, and biochemical studies demonstrated a defect in pre-rRNA maturation as a result of the mutation. Our findings are important as for the first time germline mutation of RPS20 is linked to hereditary colon cancer susceptibility and predisposition to human disease overall. The results show the power of the approach used and encourage investigations of additional FCCX families for mutations in RPS20 and other similar genes. Danish families will be the first non-Finnish families to be tested in this regard.

The accumulating evidence shows that many tumor suppressor genes can be inactivated by genetic or epigenetic mechanisms (**Peltomäki, Clin Genet 85: 403 – 412, 2014**). We have identified CpG islands in the promoter regions of BMPR1A and RPS20, and are currently addressing the possibility of constitutional epimutations in FCCX families without genetic mutations.

The clinical phenotype of FCCX sometimes overlaps with families exhibiting colorectal cancer and a variable number of polyps. Targeted re-sequencing of polyposis families resulted in the identification of a novel deletion affecting the minor APC promoter 1B in a family with unbalanced expression of APC transcripts (**Pavicic et al., Genes Chrom Cancer 53: 857-864, 2014**). The results outline a strategy to dissect "hidden" alterations in established colon cancer-associated genes as causes of inherited colon cancer susceptibility.

In Denmark, the CRC1000 database has been updated. Selection of the most informative families and collection of samples from the CRC1000 cohort for molecular studies are in progress. Linkage analysis has pinpointed a strong candidate for a new colon cancer susceptibility locus in an extended Danish family (**Rudkjoebing et al., submitted**). Efforts to identify the responsible gene by next generation sequencing and other methods are underway.

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

Our research has identified a novel colon cancer susceptibility gene. The finding is important for both basic science and translational applications, since it pinpoints a new pathway, ribosome biosynthesis and function, in colon tumorigenesis. The identification of a strong predisposing mutation in a given family offers a molecular tool to recognize family members who are at increased cancer risk. The enrolment of mutation carriers in active cancer prevention by regular colonoscopy screening and other means is expected to reduce colon cancer-associated morbidity and mortality. At the same time, family members who turn out to be non-carriers can be exempted from unnecessary surveillance and unfounded fear of cancer.

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

High-penetrance mutations in novel genes are expected to be relatively rare on a population level. A joint study of colon cancer families from the Finnish and Danish cohorts is highly advantageous because it increases the likelihood of finding susceptibility genes that might be shared by several families. The discovery of a likely susceptibility gene in colon cancer families from one population will immediately make it possible to evaluate the prevalence, pathogenicity, and clinical significance of the alteration in similar families from another Nordic population, which is crucial to determine the broader impact of the findings.

5. Publications resulting from the NCU research grant

1. Nieminen TT, O'Donohue M-F, Wu Y, Lohi H, Scherer SW, Paterson AD, Ellonen P, Abdel-Rahman WM, Valo S, Mecklin J-P, Järvinen HJ, Gleizes P-E, **Peltomäki P**. Germline mutation of RPS20, encoding a ribosomal protein, predisposes to hereditary nonpolyposis colorectal carcinoma without DNA mismatch repair deficiency. Gastroenterology 147: 595-598 (2014).

2. Pavicic W, Nieminen T, Gylling A, Pursiheimo J-P, Laiho A, Gyenesei A, Järvinen HJ, **Peltomäki P**. Promoter-specific alterations of APC are a rare cause for mutation-negative familial adenomatous polyposis. Genes Chrom Cancer 53: 857-864 (2014).

3. **Peltomäki P.** Epigenetic mechanisms in the pathogenesis of Lynch syndrome. Clin Genet 85: 403 – 412 (2014).