Søknadsinformasjon

Utlysning	Nordic Cancer Union Research Grant, 2014
Søknad	Search for novel high-penetrance susceptibility genes for familial cancer from Finnish and Danish cohorts
Søknadsid	154629
Innsendt av	Päivi Peltomäki

Oppgave: Progress report

Tilordnet	Päivi Peltomäki
Status	Arkivert
Opprettet	04.02.2016

RAPPORT

Briefly describe the project in a language understandable to non-scientists

The Finnish and Danish nationwide registries have revealed extensive clusters of colorectal cancer families, some of which are clearly hereditary. This project focuses on a new entity of hereditary colon cancer without polyposis, known as Familial Colorectal Cancer Type X (FCCX). We aim to investigate 100 FCCX families from the Finnish and Danish cohorts to determine the prevalence of mutations in two recently discovered susceptibility genes and to identify novel predisposing genes in families remaining mutation-negative, so far. Our research increases the understanding of colorectal tumorigenesis and offers new tools for targeted cancer prevention in high-risk families.

Summarize the major findings of the project

A new high-penetrance colon cancer predisposition gene, RPS20 encoding a component (S20) of the small ribosomal subunit, was identified by genetic linkage analysis, exome sequencing, tumor studies, and functional investigations (Nieminen et al. 2014 and 2015). A truncating germline mutation co-segregated with colon cancer in a four-generation FCCX family from Finland and was associated with a defect in pre-rRNA maturation. Our findings demonstrate for the first time that mutations in a gene encoding a ribosomal protein can predispose individuals to microsatellite-stable colon cancer. Recently, genetic linkage analysis in an extended Danish family mapped a new susceptibility locus to a region on chromosome 11q24; the same region has been suggested by two earlier studies (Rudkjøbing et al. 2015). Efforts to identify the causative gene are underway. Apart from genetic mechanisms, we consider the possibility of epigenetic (regulatory) mechanisms in mutation-negative families (Kaur et al. 2015, Valo et al. 2015, Joensuu et al. 2015). Collectively, the findings described above imply that FCCX is molecularly heterogeneous and encourage further studies to define its molecular basis.

Describe how the project has increased our knowledge of the prevention, cause and/or cure for cancer

Our research has identified a novel colon cancer susceptibility gene (RPS20) and mapped a new chromosomal locus for colon cancer predisposition (11q24). By suggesting new pathways for colon tumorigenesis, the findings are important for both basic science and translational applications. 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.

Outline how Nordic cooperation has added value to this project

While high-penetrance mutations can give rise to extensive colorectal cancer families, such mutations are expected to be relatively rare on a population level. A joint study of colon cancer families from the Finnish and Danish cohorts 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.

List the publications resulting from the NCU research grant

Author(s), title, journal and edition	PMID (8 digits, only if possible)
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).	24941021
Nieminen TT, Mecklin J-P, Järvinen HJ, Peltomäki P. Reply (RE: Ribosomy association with colorectal cancer by Kessel R, Vlachos A, and Lipton JM ibid). Gastroenterology 148: 259 (2015).	25451653
Kaur S, Lotsari JE, Al-Sohaily S, Warusavitarne J, Kohonen-Corish M, Peltomäki P. Identification of subgroup-specific miRNA patterns by epigenetic profiling of sporadic and Lynch syndrome-associated colorectal and endometrial carcinoma. Clin Epigenet 7: 20 (2015).	25767621
Valo S, Kaur S, Ristimäki A, Renkonen-Sinisalo L, Järvinen H, Mecklin J-P, Nyström M, Peltomäki P. DNA hypermethylation appears early and shows increased frequency with dysplasia in Lynch syndrome-associated colorectal adenomas and carcinomas. Clin Epigenet 7: 71 (2015).	26203307
Joensuu EI, Nieminen TT, Lotsari JE, Pavicic W, Abdel-Rahman WM, Peltomäki P. Methyltransferase expression and tumor suppressor gene methylation in sporadic and familial colorectal cancer. Genes Chrom Cancer 54: 776 – 787 (2015).	26305882
Rudkjøbing LA, Eiberg H, Mikkelsen HB, Binderup ML, Bisgaard ML. The analysis of a large Danish family supports the presence of a susceptibility locus for adenoma and colorectal cancer on chromosome 11q24. Fam Cancer 14: 393 – 400 (2015).	25724759

Brief overview of expenditures for last year 1 vedlegg (Expenditures for 2015.pdf)

Peltomäki & Bisgaard: Expenditures for 2015

The NCU grant was used to cover expenses arising from research activities described in the proposal. The Finance Unit of Helsinki University was responsible for the financial management of this project, and original documentation of expenditures is available through the University's accounting system, if needed.

Expenditures (2015)	Amount (€)	
Salaries	19 015,99	
Reagents	6 217,09	
Consumables	303,55	23 692,51
Other material costs	17 171,87	
Overhead (15%)	6 259,39	
Total	**48 967,89**	
Grant award for 2015	60 000, 00	
Carry-over from 2014	2 396,42	
Balance (December 31st, 2015)	13 428,53	

Salary costs consist of employment of a postdoctoral researcher (Taina Nieminen, Helsinki University) for 4 months. Reagents include chemicals, enzymes, and kits for genetic, methylation, and expression analyses. Consumables include pipette tips, test tubes, and other similar supplies. Other material costs include next generation sequencing services purchased from the FIMM Technology Center (15 454, 19 EUR) and a software license for data analysis (Golden Helix, 1 624, 73 EUR).

The surplus (13 428, 53 EUR) will be used for the project in 2016.