Søknadsinformasjon

Utlysning	Nordic Cancer Union Research Grant, 2015
Søknad	Search for Novel High-Penetrance Susceptibility Genes for Familial Colorectal Cancer from Finnish and Danish Cohorts
Søknadsid	176392
Innsendt av	Päivi Peltomäki

Oppgave: Progress report

Tilordnet	Päivi Peltomäki
Status	Løst
Opprettet	10.02.2017

RAPPORT

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

The Nordic nationwide registries reveal extensive clusters of colorectal cancer families, some of which show the hallmarks of hereditary cancer. This project focuses on a new entity of hereditary colon cancer without polyposis, known as Familial Colorectal Cancer Type X (FCCX). Close to 100 FCCX families have been investigated 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

Our combined approach of genetic linkage analysis, exome sequencing, tumor studies, and functional investigations identified a new high-penetrance colon cancer predisposition gene, RPS20, which encodes a component (S20) of the small ribosomal subunit (Nieminen et al. 2014 and 2015). A truncating germline mutation co-segregated with microsatellite-stable 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 FCCX can be a ribosomopathy. Our observation of RPS20 being associated with increased colon cancer risk was later confirmed by other investigators who studied families from a non-Finnish population (Broderick P et al., Gastroenterology 152: 75 – 77, 2017). 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 (Abdel-Rahman et al. 2016). To date, 54 representatives of FCCX families have undergone a complete exome sequencing, and a number of high- and low-penetrance mutations in novel and established colon cancer genes have been identified (our unpublished data). Parallel next-generation sequencing of polyposis families (Nieminen et al. 2016) has revealed some molecular overlap but the sharing of predisposition genes with FCCX is generally limited. Collectively, the findings imply that FCCX is molecularly heterogeneous and further studies to define its molecular basis are warranted.

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), pinpointed a number of worthwhile candidate genes, and mapped a new chromosomal locus for colon cancer predisposition (11q24). 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 can 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. The discovery of new pathways for colon tumorigenesis stimulates research to target these pathways for diagnostic, preventive, and therapeutic applications.

Outline how Nordic cooperation has added value to this project

Mutations associated with high life-time risks of cancer can provide valuable tools for scientific and translational applications, but are typically 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 populations. The discovery of a likely susceptibility gene in colon cancer families from one population will immediately make it possible to extend the studies to another population, which is crucial to evaluate the prevalence, pathogenicity, and clinical significance of the findings.

List the publications resulting from the NCU research grant

Author(s), title, journal and edition	PMID (8 digits, only if possible)
Koskenvuo L, Peltomäki P, Renkonen-Sinisalo L, Gylling A, Nieminen TT, Ristimäki A, Lepistö A. Desmoid tumour patients carry an elevated risk of familial adenomatous polyposis. J Surg Oncol 113: 209 – 212 (2016)	26663236
Abdel-Rahman WM, Lotsari-Salomaa JE, Kaur S, Niskakoski A, Knuutila S, Järvinen H, Mecklin J-P, Peltomäki P. The role of chromosomal instability and epigenetics in colorectal cancers lacking -catenin/TCF regulated transcription. Gastroenterol Res Practice 2016: 6089658 (2016)	27047543
Nieminen TT, Pavicic W, Porkka N, Kankainen M, Järvinen HJ, Lepistö A, Peltomäki P. Pseudoexons provide a mechanism for allele-specific expression of APC in familial adenomatous polyposis. Oncotarget 7: 70685 – 70698 (2016)	27683109
Peltomäki P. Update on Lynch Syndrome Genomics. Fam Cancer 15: 385 – 393 (2016)	26873718
Abdel-Rahman WM, Faris ME, Peltomäki P. Molecular determinants of colon cancer susceptibility in the East and West. Current Molecular Medicine (2016, in press)	

Brief overview of expenditures for last year 1 vedlegg (Brief overview of expenditures-Peltomäki.pdf)

Peltomäki & Bisgaard NCU grant

	Amount (€)
Carry-over from 2015	13 427, 94
Grant award for 2016	60 000, 00
Expenditures (2016)	
Salaries	16 812,89
Reagents	1 354,08
Consumables	158,97
Other material costs*	44 088,32
Overhead (15%)	11 013,68
Total	**73 427,94**
Balance (December 31st, 2016)	0,00

*Other material costs include next-generation sequencing (targeted, exome & RNA-seq).