Prevention, Detection and Molecular Characterisation of Mismatch Repair-Related Hereditary Cancers of the Digestive System

Keywords
HNPCC, familial gastric cancer, mismatch repair

Summary
This project focuses on hereditary cancers of the digestive system associated with microsatellite instability; hereditary non-polyposis colorectal cancer (HNPCC) and familial gastric cancer (FGC). Microsatellite instability is the result of a defective mismatch repair (MMR) system. Germline mutations in MMR genes are found in families with HNPCC characterised by development of colorectal cancer and extracolonic malignancies, particularly cancer of the endometrium. Evidence is accumulating that also a subset of FGC is MMR-related as families have been identified with tumours showing microsatellite instability. MMR gene mutations have not yet been identified in these families.

Problem
In HNPCC, identification of MMR gene mutations has helped in identifying individuals at risk when a clear pathogenic mutation was found. Many families, however, in particular those with less penetrant HNPCC, remain genetically unresolved. Furthermore, in a large proportion of families, mutations are identified whose pathogenic nature is uncertain (unclassified variants). Although we have made great progress in the genetic delineation of this cancer syndrome, it has scarcely improved early diagnosis or treatment of cancer.

Aim
The objectives are to improve genetic testing by:
• determining the role known MMR genes play in both cancer syndromes and identifying new HNPCC or FGC-related genes
• setting up comprehensive functional assays to determine the role of unclassified variants in MMR related genes
• identifying tumour cells at very early stages in faeces by enhancing the sensitivity of MSI determination
• profiling mutations accumulating in tumours as a consequence of MMR deficiency, in order to get a better insight in tumour development, which can be instrumental in clinical management/tumour treatment.

Expected results
Our proposal will thus improve genetic testing, improve early detection of polyps/tumours in individuals at risk for these cancer syndromes and improve clinical management of HNPCC and FGC patients.

Potential applications
The assays and the data generated will be set up and used in diagnostic laboratories and by clinical geneticists all over Europe and the world.

Project website: under construction

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Coordinator

Robert M.W. Hofstra
University Medical Center Groningen
Department of Medical Genetics
Groningen, The Netherlands
E-mail: r.m.w.hofstra@medgen.umcg.nl

Partners

Lauri A. Aaltonen
Haartman Institute
Department of Medical Genetics
Helsinki, Finland
E-mail: lauri.aaltonen@helsinki.fi

Lene Juel Rasmussen
Roskilde University
Department of Life Sciences and Chemistry
Roskilde, Denmark
E-mail: ljr@ruc.dk

Niels de Wind
Leiden University Medical Center
Department of Toxicogenetics
Leiden, The Netherlands
E-mail: n.de_wind@lumc.nl

Raquel Seruca
University of Porto
Institute of Molecular Pathology and Immunology
Cancer Genetics Group
Porto, Portugal
E-mail: rseruca@ipatimup.pt