A genetic variant in *telomerase reverse transcriptase (TERT)* modifies cancer risk in Lynch syndrome patients harbouring pathogenic *MSH2* mutations

Bente A. Talseth-Palmer[1,2] , Tiffany-Jane Evans[1], Sami Belhadj[3], Katherine A. Bolton[1], Dagmara Dymerska[4], Shantie Jagmohan-Changur[5], Grzegorz Kurzawski[4], Juul T. Wijnen[5], Laura Valle[3], Hans F.A Vasen[7], Jan Lubinski[4] and Rodney J. Scott[1, 8]

[1] School of Biomedical Science and Pharmacy, Faculty of health and Medicine, University of Newcastle and Hunter Medical Research Institute, Newcastle, Australia
[2] Research and Development Unit, Møre and Romsdal Hospital Trust, Molde, Norway
[3] Hereditary Cancer Program, Catalan Institute of Oncology, IDIBELL and CIBERONC, Hospitalet de Llobregat, Barcelona, Spain
[4] Hereditary Cancer Center, Pomeranian Medical University, Szczecin, Poland
[5] Department of Human Genetics, Leiden University Medical Center, Leiden, the Netherlands
[6] Department of Clinical Genetics, Leiden University Medical Center, Leiden, the Netherlands
[7] Department of Gastroenterology and Hepatology, Leiden University Medical Center, Leiden, the Netherlands
[8] NSW Health Pathology, Newcastle, NSW, Australia

Background: Individuals with Lynch syndrome (LS), an autosomal dominant inherited cancer syndrome caused by mutations in DNA mismatch repair genes have an increased risk of developing a range of epithelial malignancies, in the absence of a pre-malignant phenotype. Common genetic variants of the TERT gene are associated with telomere length and have been linked to a wide range of cancers, including colorectal cancer (CRC) and with tumours arising in LS.

Aim: In this study we have genotyped 3 SNPs in *TERT*; rs2736108 (upstream gene variant), rs2075786 and rs7705526 (both intronic variants), previously shown to influence telomere length in tumours and in association with LS.

Methods: We genotyped 1895 LS patient samples for rs2075786 (G>A) and 1241 LS patient samples for rs2736108 (C>T) and rs7705526 (C>A) using TaqMan SNP assays (Applied Biosystems). The risk of cancer with each SNPs' genotype was estimated by heterozygous and homozygous odds ratio (OR) using simple logistic regression and mixed-effects logistic regression to adjust for gene, gender and country taking into account family ID (probands and relatives).

Results: We observed an increased risk of cancer in patients carrying pathogenic *MSH2* mutations and the heterozygous genotype (GA) for rs2075786 (OR=1.84, confidence interval (CI) =1.15-2.94), p=0.01). This association is even stronger if patients <45 years of age at diagnosis were compared to cancer free patients; *MSH2* and GA for rs2075786 (OR=2.53, CI=1.43-4.49, p=0.002).

Conclusion: Even though both *MLH1* and *MSH2* mutation carrier's initially have similar risks of cancer, a SNP in *TERT* appears to be associated with a differential risk of developing cancer for *MSH2* mutation carriers. *MSH2* deficiency alone has previously been shown to accelerate telomere shortening in normal human cells and can explain the increased risk in younger heterozygous *MSH2* mutation carriers. By including modifier gene/loci in risk algorithms it should be possible to tailor surveillance options for individual patients.