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

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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.