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After eight years of searching for modifier genes affecting disease expression in lynch syndrome - where are we now?

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Rationale: Lynch syndrome (LS) is an autosomal dominantly inherited cancer syndrome caused by mutations in DNA mismatch repair (MMR) genes and is characterised by early-onset epithelial cancers. The most recent disease-penetrance estimation in LS suggest that, by age 70 years, 33-53% will develop colorectal cancer (CRC) and 44% of women will develop endometrial cancer. Individuals with LS have an increased risk of developing malignancies, but a pre-malignant phenotype does not exist.

Objective: The purpose of this study was to investigate candidate genes/regions conferring an altered susceptibility to disease expression in LS patients. If additional genetic factors influencing disease risk are identified a more personalised screening program can be set in place, which will lower the mortality of the disease and provide insight into the molecular mechanisms underlying LS.

Methods and Results: Candidate single-nucleotide polymorphisms (SNPs) have been chosen on the basis of functional significance, candidate pathways for disease development or previously reported associations. In earlier reports (2005-2007) the sample numbers used in such studies was in order of ~200 samples and controversial results was the rule rather than the exception. Today the sample sizes have increased to >1300 thereby increasing the reliability of any detected association. The results now demonstrate identification of low-penetrant CRC susceptibility loci that modify disease risk in *MLH1* mutation carrier.

Conclusion: As a result of increasing sample size by expanding international collaborations, we have demonstrated that even though both *MLH1* and *MSH2* mutation carriers starts off with the same risk of CRC, other genetic factors are also associated with a differential risk of developing CRC, specifically for *MLH1* mutation carriers. By including modifier gene/loci in risk algorithms it should be possible to tailor surveillance options for individual patients, which should allow for better outcomes in terms of patient uptake resulting in reduced morbidity and mortality.

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