[2]Institute of Health Policy, Management and Evaluation, Joint Centre for Bioethics, University of Toronto, Toronto, Ontario, Canada
E-mail: fiona.miller@utoronto.ca

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8q23.3 and 11q23.1 as modifying loci influencing the risk for CRC in Lynch syndrome

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Recently, Houlle *et al*[1] reported results of two modifier SNPs in Lynch syndrome, rs16892766 on 8q23.3 and rs3802842 on 11q23.1 previously identified as low-susceptibility colorectal cancer (CRC) loci, challenging earlier reported findings.[2,3]

In 2009 Wijnen *et al*[2] demonstrated that two SNPs located on 8q23.3 (rs16892766) and 11q23.1 (rs3802842) were associated with an increased risk of developing CRC in Dutch Lynch syndrome patients. The study revealed that patients' homozygote for SNP rs16892766 were associated with an elevated risk of CRC in a dose-dependent manner with a 2.16-fold increased risk of developing CRC, whereas the variant (CC) genotype of SNP rs3802842 was associated with an increased risk of CRC in female carriers only (HR=3.08).[2] In a combined analysis of the two SNPs, the risk was significantly associated with the number of risk alleles and the effect was shown to be stronger in female carriers than in male carriers.

Recently, Talseth-Palmer *et al*[3] confirmed the increased risk of CRC in Lynch syndrome patients in a combined Australian and Polish sample cohort but only in *MLH1* mutation carriers. In this study the two Lynch syndrome populations (Australian and Polish) were analysed separately and together, as a larger sample size gives increased power and more reproducible results. SNP rs3802842 revealed a significant association on the risk of developing CRC in the combined sample population (Australian and Polish) with a HR of 2.67. When analysed separately, the Australian sample population displayed significant results whereas the Polish sample population displayed a trend, which demonstrates the increased power acquired when more samples are analysed together. SNP rs16892766 was only significantly associated with the increased risk of CRC in Australian *MLH1* mutation carriers, but as this was the same SNP that displayed an association in the Dutch study[2] we also analysed the additive effect of the two SNPs. We were able to show that *MLH1* mutation carriers from Australia and Poland harbouring three risk alleles for the two SNPs developed CRC on average 24 years younger and were at 5.52-fold increased risk of CRC compared with individuals harbouring no risk alleles. The quote in the report by Houlle *et al*[1] 'During the submission of this study, Talseth-Palmer *et al*[15] reported that in *MLH1* carriers, but not in *MSH2* carriers, the 11q23.1 CC and 8q23.3 AC genotypes were associated with an increased risk, but this significant association detected in 373 Australian mutation carriers was not found in 311 Polish mutation carriers analysed in the same study' is incorrect, as we did see this association in our combined sample cohort.

A decreased risk of CRC (HR=0.267, P=0.0271) for the CC (variant) genotype for SNP rs16892766 is reported by Houlle *et al*.[1] According to previously published results discussed above this result is contradictory. A decreased risk of CRC indicate a later age of onset of CRC in the two individuals who harboured the CC genotype for SNP rs16892766, but the age of onset of CRC of these two individuals was not reported and can therefore not be commented on. It is highlighted by the French authors that the small number of subjects harbouring this genotype could affect the reported results. We believe that the observed results could be due to the fact that either of these two individuals harbours the variant (CC) genotype for SNP rs3802842, which seems to be important for the increased risk of CRC as observed in the Australian/Polish sample cohort.

A meta-analysis of the French and Dutch data set was performed by Houlle *et al*[1] indicating that SNP rs3802842 at 11q23.1 is not associated with increased risk of developing CRC, and the only association observed in this meta-analysis was a decreased risk of CRC for SNP rs16892766 in male mutation carriers, which contradicts previously reported results.[2,3] SNP rs16892766 (8q23.3) did not show an association with the CC (variant) genotype for the overall sample size as shown on the Forest plot (Figure 1[1]), which is not surprising as positive and negative results combined will end up with a neutral result. But false positive results in the Dutch study[2] and false negative

results in the French study[1] cannot be ruled out as a reason for the neutral results observed in the meta-analysis. Also, the heterogeneity of the population (ie, *MMR* gene) is not taken into account when a meta-analysis is performed and as shown by Talseth-Palmer *et al*[3] this can drastically affect the observed results.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Bente A Talseth-Palmer[1,2], Rodney J Scott[1,2], Hans FA Vasen[3] and Juul T Wijnen[4]
[1]*School of Biomedical Sciences and Pharmacy, University of Newcastle, Newcastle, New South Wales, Australia;*
[2]*Hunter Medical Research Institute, John Hunter Hospital, Newcastle, New South Wales, Australia;*
[3]*Dutch Foundation for the Detection of Hereditary Tumours, Leiden, The Netherlands;*
[4]*Center of Human and Clinical Genetics, Leiden University Medical Centre, Leiden, The Netherlands.*
E-mail: Bente.Talseth-Palmer@newcastle.edu.au

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Reply to Talseth-Palmer *et al*

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Following the publication of our article entitled 'Evaluation of Lynch syndrome modifier genes in 748 MMR mutation carriers'[1] in which we reported that in MMR mutation carriers 8q23.3 and 11q23.1 polymorphic alleles were not significantly associated with an increased colorectal cancer (CRC) risk, Talseth-Palmer *et al*[2] indicated that we did not correctly report their results by indicating: 'During the submission of this study Talseth-Palmer *et al* reported that in *MLH1* carriers, but not in *MSH2* carriers, the 11q23.1 *CC* and 8q23.3 *AC* genotypes were associated with an increased risk, but this significant association detected in 373 Australian mutation carriers was not found in 311 Polish mutation carriers analysed in the same study'. Their study was indeed performed in two distinct samples of MMR mutation carriers, originated from Australian and Polish families, respectively.[2] As indicated in Figure 1C of their article, the variation in CRC risk according to the 11q23.1 *CC* genotype was not statistically significant in the Polish sample cohort, but only a trend was observed (log-rank P=0.1336; Wilcoxon P=0.1109, and tware P=0.117). Moreover, the variation in CRC risk according to the 8q23.1 genotype was significant only in the Australian sample whereas no results are reported for the combined sample or the Polish sample, likely pointing to non-significant results. Therefore, our comment is appropriate. Moreover, the combination of the Australian and Polish MMR mutation carrier performed in their study amounts to a meta-analysis using pooled data from two different populations. Finally, all significant differences reported were restricted to *MLH1* mutation carriers and no results were reported for *MSH2* mutation carriers or for all subjects, which also raises questions on the real impact of the 8q23.3 and 11q23.1 genotypes on the CRC risk in MMR mutation carriers. Therefore, the title of their article 'Colorectal susceptibility loci on chromosome 8q23.3 and 11q23.1 as modifiers for disease expression in Lynch syndrome' appears too broad. We do not agree with their conclusion suggesting that 8q23.3 and 11q23.1 genotyping might have a clinical utility in *MLH1* mutation carriers.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

Solene Houlle[1,2], Françoise Charbonnier[1,2], Estelle Houivet[3], Julie Tinat[1,2], Marie-Pierre Buisine[4], Olivier Caron[5], Jacques Benichou[3], Stéphanie Baert-Desurmont[1,2] and Thierry Frebourg[1,2]
[1]*Inserm U614, Faculty of Medicine, Institute for Biomedical Research and Innovation, University of Rouen, Rouen, France;*
[2]*Department of Genetics, University Hospital, Rouen, France;*
[3]*Department of Biostatistics and Inserm U657, University Hospital, Rouen, France;*
[4]*Laboratory of Molecular Biology, University Hospital, Lille, France;*
[5]*Department of Medicine, Institut Gustave Roussy, Villejuif, France*
E-mail: Frebourg@chu-rouen.fr

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Association study of the single nucleotide polymorphisms of *PARK2* and *PACRG* with leprosy susceptibility in Chinese population

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Leprosy is a chronic infectious disease caused by *Mycobacterium leprae*, affecting both the skin and peripheral nerves. It has long