Modifier Genes in Lynch Syndrome: Functional Genomics and its Consequence on Disease Expression

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Declaration

This thesis contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. I give consent to this copy of my thesis, when deposited in the University Library, being made available for loan and photocopying subject to the provisions of the Copyright Act 1968.

28-March-2012

Date Stuart Reeves
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## Common Abbreviations

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<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>CRC</td>
<td>Colorectal Cancer</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic Acid</td>
</tr>
<tr>
<td>DNMT3B</td>
<td>DNA Methyltransferase 3 Beta</td>
</tr>
<tr>
<td>HNPCC</td>
<td>Hereditary nonpolyposis Colorectal Cancer</td>
</tr>
<tr>
<td>hMLH1</td>
<td>Human MutL Homolog 1</td>
</tr>
<tr>
<td>hMSH2</td>
<td>Mut S Homolog 2</td>
</tr>
<tr>
<td>IGF-1</td>
<td>Insulin like Growth Factor 1</td>
</tr>
<tr>
<td>MMR</td>
<td>Mismatch Repair</td>
</tr>
<tr>
<td>MTHFR</td>
<td>Methylene-tetrahydrofolate Reductase</td>
</tr>
<tr>
<td>PCR</td>
<td>Polymerase Chain Reaction</td>
</tr>
<tr>
<td>RNA</td>
<td>Ribonucleic Acid</td>
</tr>
<tr>
<td>SNP</td>
<td>Single Nucleotide Polymorphism</td>
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Publications


Abstract

Colorectal cancer (CRC) is globally a major cause of morbidity and mortality. Each year more than one million patients will be diagnosed with colorectal cancer, with about 15 - 20% of these patients having a family history or an inherited colorectal cancer syndrome. Somewhere between 1% and 7% (dependent on population under study) of these cases will have Lynch syndrome, which is the most common hereditary autosomal-dominant inherited cancer syndrome caused by germline mutations in deoxyribonucleic acid (DNA) mismatch repair genes.

Patients diagnosed with Lynch syndrome who harbour a confirmed germline mutation in DNA mismatch repair (MMR) genes have an 80% lifetime risk of developing an epithelial malignancy. Each patient belongs to a family that requires special medical attention including genetic counselling, DNA testing for mismatch repair genes (most frequently hMLH1 or hMSH2) and screening for CRC.

There is, however, considerable variation in the age of disease onset which is explained by a combination of genetic and environmental factors. The studies described in this thesis are aimed to better understand the genetic modifying effects on disease expression and how they relate to the likely age of colorectal cancer onset.

Previous studies have identified a polymorphic CA repeat region in IGF-1 and two specific single nucleotide polymorphisms in MTHFR that were thought to alter the age of disease onset in individuals with Lynch syndrome. The effects of these
polymorphisms were examined in larger multinational cohorts of patients and found to have significant effects on disease onset age. This is discussed in chapters 2, 3 and 4.

Another similar study had identified a single nucleotide polymorphism in DNMT3B which was reported to have a significant effect in colorectal cancer expression in Lynch syndrome. The effect of this polymorphism was examined in a large multinational cohort of patients however, it was found to have no effect on the age of disease onset. Several candidate polymorphisms were also identified in the DNA repair genes BRCA2, hMSH3, Lig4, hOGG1, XRCC1, XRCC2 and XRCC3 but no significant associations were identified. The results from these studies are discussed in chapters 5 and 6.

All data generated from these studies were extensively analysed by a combination of statistical tests that included Kaplan-Meier survival and Cox hazard regression analysis allowing data to be stratified by both single and multi variable factors. Allele frequencies were also tested for significant deviation from the Hardy-Weinberg equilibrium, while Pearson’s Chi-square test was utilised to evaluate differences in the allele frequencies between the multinational cohort groups and distribution of genotypes.

The results described in this thesis contribute to a better understanding of disease expression in Lynch syndrome as it identifies genetic factors involved in the etiology of malignancy in this disease. The progress made in this area of medical research will aid in providing better predictive information of greater accuracy regarding the risks of colorectal cancer and enable the development of personalised cancer surveillance regimens.