THE ROLE OF THE XPF GENE POLYMORPHISM (XRCC4) SER835SER IN THE RISK OF MALIGNANT TRANSFORMATION OF CELLS IN THE COLORECTAL CANCER*

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Participation of DNA repair systems in the pathogenesis of cancer has been a suspected phenomenon for a long time. Decreased efficiency in DNA repair translates to their ability to fix and consequently leads to mutations and the process of carcinogenesis. Linking individual polymorphisms of DNA repair systems with an increased risk of colorectal cancer will allow the classification of patients to high-risk groups and their placement under preventive program.

The aim of the study was to determine the effect of XPF gene polymorphism Ser835Ser on increasing the risk of colorectal cancer in the Polish population.

Material and methods. As the material blood collected from 146 patients diagnosed with colon cancer was used. The control group consisted of 149 healthy subjects. Genotyping was performed by Taq-Man method.

Results. The results indicate that genotype TCC/TCT is associated with a decreased risk of colorectal cancer (OR 0.574; CI 95% 0.335-0.984; p=0.043).

Conclusions. Based on these results, we conclude that the XPF gene polymorphism Ser835Ser may be associated with a decreased risk of colorectal cancer.

Key words: colorectal cancer, XRCC4, XPF, DNA repair

Of all types of colorectal cancer it appears that sporadic cancers are most difficult to determine their aetiology. There are no clear indications clearly predisposing to the disease what makes its etiology remains unknown. Role of genetic factors have long been suspected as one of the causes of sporadic CRC, and going in this direction research confirms that genes polymorphisms in DNA repair systems can significantly modulate the efficiency of repair damage and by that modifying the risk of cancer. One of such system is the nucleotide excision repair (NER), which removes the damage caused by physical and chemical factors by cutting the damaged nucleotide. In the NER pathway damage is recognized by the XPA protein and then a DNA fragment of about 30 bp is removed by endonuclease. The removed part is replaced by a precise base pairing, and the newly synthesized segments are joined by ligase. One of the key endonuclease in this process is that encoded by the XPF gene (XRCC4). Change in the level of enzyme activity may directly translate into damage removal efficiency throughout the NER pathway, and consequently lead to a potential fixation of mutations and neoplastic transformation of the cell. Therefore, suspected to be the XPF gene polymorphisms may affect the modulation of the risk of CRC.

The aim of this study was to determine the effect of XPF gene polymorphism Ser835Ser
on the risk of colorectal cancer in the Polish population.

MATERIAL AND METHODS

Experimental material

Test DNA was isolated from peripheral blood samples collected from 146 unrelated patients. All patients had histologically confirmed colorectal cancer. The study group consisted of 76 men and 70 women (mean age 61 ± 8). To assess the stage of cancer TNM scale was used. A detailed information about the patients illustrates tab. 1. The control group consisted of 149 persons age corresponding to the study group who did not have cancer.

Methods

DNA isolation was performed with commercial kit QIAamp DNA Blood Mini Kit for isolation of high-molecular-weight DNA (Qiagen). The distribution of polymorphic variants Xpf Ser835Ser was examined using TaqMan method. Test polymorphism refSNP is 1799801.

Statistical analysis

The resulting number of each genotype was compared with the expected value based on Hardy-Weinberg equilibrium. The significance of differences between the frequencies of alleles and genotypes between groups was assessed using $\chi^2$ test. The risk of an event was assessed using multivariate regression analysis (odds ratio, OR) with corresponding confidence interval 95% (CI 95%).

RESULTS

Table 2 presents the analysis of the distribution of polymorphic variants of the gene XPF Ser835Ser and their correlation with the modulation of the risk of colon cancer. Studies indicate that genotype TCC/TCT may affect the decreased risk of CRC (OR 0.574; CI 95% 0.335-0.984; $p=0.043$).

DISCUSSION

Determining the indisputable impact of genes polymorphisms of MMR (Mismatch repair) repair pathway on the Hereditary non-polyposis colorectal cancer (HNPCC) paved the way for the typing of patients with increased predisposition to CRC incidence (1, 2). The next step is to establish the following relationship between genes of other DNA repair systems and modulation of cancer. In the case of repair of NER mechanism studies indicate the potential compound with a variety cancers: bladder cancer (3) lung cancer (4), breast cancer (5) and the head and neck cancer (6). The enzyme encoded by the tested XPF is designated primarily as a factor in modulating the risk of lung cancer (7, 8) and breast cancer (9). In most

<table>
<thead>
<tr>
<th>Patients</th>
<th>Sex</th>
<th>Stage of tumor according to TNM classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=146</td>
<td></td>
<td>T</td>
</tr>
<tr>
<td>146</td>
<td>70</td>
<td>76</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Genotype/Allel</th>
<th>Patients n=146</th>
<th>Controls n=149</th>
<th>OR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCC/TCC</td>
<td>51</td>
<td>42</td>
<td>1 (ref)</td>
<td>-</td>
</tr>
<tr>
<td>TCC/TCT</td>
<td>53</td>
<td>76</td>
<td>0.574 (0.335-0.984)</td>
<td>0.043</td>
</tr>
<tr>
<td>TCT/TCT</td>
<td>42</td>
<td>31</td>
<td>1.116 (0.601-2.070)</td>
<td>0.729</td>
</tr>
<tr>
<td>TCC</td>
<td>155</td>
<td>160</td>
<td>1 (ref)</td>
<td>-</td>
</tr>
<tr>
<td>TCT</td>
<td>137</td>
<td>138</td>
<td>1.025 (0.742-1.416)</td>
<td>0.888</td>
</tr>
</tbody>
</table>
cases, no association was found between polymorphisms of XPF and CRC (10). In contrast, the study results indicate a protective effect of genotype TCC / TCT since it reduces the risk of colorectal cancer. There is no literature data for the tested polymorphism in the field of colorectal cancer, but this effect was observed earlier times for other polymorphisms (11, 12, 13). This is probably related to changes in enzyme activity resulting in increased efficiency of repairing the damage. In addition, one should consider the complexity of the process of carcinogenesis at which greatly effect have intergenic interactions that may significantly alter the level of risk – taken individually polymorphisms do not affect the modulation of risk, but after an analysis of the impact of gene-gene interactions it appears to be a factor increasing or reducing the risk of cancer (14, 15). Therefore, we believe that further studies that may establish indisputable link between the studied gene polymorphism and the risk of colorectal cancer are necessary.

CONCLUSION

Based on these results, we conclude that the XPF gene polymorphism Ser835Ser may be associated with a decreased risk of colorectal cancer.

REFERENCES


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