Computational Detection of Deleterious Single Nucleotide Polymorphisms in Human Adenomatous Polyposis Coli Gene the Gate-Keeper of Colorectal Carcinoma

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Introduction

• Colorectal cancer (CRC) is one of the most diffuse cancers worldwide; evidences showed that Adenomatous Polyposis Coli (APC) is a multifunctional tumor suppressor gene that regulates and controls many biological functions; mutations in this gene has been reported in many cases of CRC.

• Many reports proposed that SNPs in the APC gene could predispose to colorectal adenomatous phenotype and underlie the risk of colonic adenoma/carcinoma sequence; therefore this work focus on detection and analysis of functionally deleterious SNPs of APC gene prioritizing non-synonymous (nsSNP) and 3'UTR SNPs for their potentiality in cancer predisposition and prognosis using computational tools to highlight mutations underlying phenotypic variations (classical or atypical forms of a disorder) and to predict the structural and functional consequences of these polymorphisms.

Materials and Methods

• The process of selection of SNPs was prioritizing those in the coding region (exonal SNPs) that are non-synonymous (nsSNP) and SNPs at un-translated region at 3'ends (3'UTR) to predict the effect on miRNA binding on these regions that may greatly associates tumor progression. The SNPs and the related ensembles protein (ESNP) were obtained from the SNPs database (dbSNPs) for computational analysis from http://www.ncbi.nlm.nih.gov/snp/ and Uniprot database http://www.uniprot.org for related protein sequences.

• nsSNPs were then subjected to SIFT soft ware to sort intolerant (damaging) SNPs from tolerant (non-damaging) depending on cutoff value 0.05 considering the values below or equal to 0.0_0.04 to be damaging; furthermore those damaging SNPs were re-analyzed by Polyphen software which predicts the effect of amino acid substitution on both structure and function of a human protein by analysis of multiple sequence alignment and protein 3Dstructure.

Results

• 333 nsSNPs were analyzed by tools that concerning structural and functional aberrations and measure degrees and scores of alterations; and then the protein variants were subjected to structural modeling to highlight the impact of amino acid substitution upon protein phenotype. Analysis with Sift and Polyphen resulted in 15 damaging nsSNPs out of the total and marked 5 amino acid substitutions (E142G, R99W, R24N, L680S and W157T) with probably high deleterious scores, while analysis of 51 3'UTR SNPs by specialized tool PolymiRTS resulted in no single nucleotide variant at that region could disturb the conserved sites of miRNA.

<table>
<thead>
<tr>
<th>SNP ID</th>
<th>Nucleotide change</th>
<th>Amino Acid change</th>
<th>SIFT Prediction &amp; Score</th>
<th>Polyphen Prediction &amp; Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs77907679</td>
<td>A/G</td>
<td>E142G</td>
<td>Damaging (0.03)</td>
<td>Probably damaging (1.000)</td>
</tr>
<tr>
<td>rs139196838</td>
<td>C/T</td>
<td>R99W</td>
<td>Damaging (0.02)</td>
<td>Probably damaging (1.000)</td>
</tr>
<tr>
<td>rs145945630</td>
<td>C/T</td>
<td>R24N</td>
<td>Damaging (-1)</td>
<td>Probably damaging (1.000)</td>
</tr>
<tr>
<td>rs137854582</td>
<td>A/T</td>
<td>L680S</td>
<td>Damaging (-1)</td>
<td>Probably damaging (1.000)</td>
</tr>
<tr>
<td>rs137854576</td>
<td>A/G</td>
<td>W157T</td>
<td>Damaging (-1)</td>
<td>Probably damaging (1.000)</td>
</tr>
</tbody>
</table>

Table1: Showing the most pathogenic SNPs with high damaging scores & probability.

Conclusions

• This work presented multiple damaging SNPs that cause truncation of APC gene product; the key factor for these aberrations was the presence of multiple pathological variants in the coding regions (nsSNPs) rather than those in the 3'UTR regions.

References
