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TP^{53} Gene Polymorphisms and its association with Colorectal Cancer: A Case-Control Investigation

Abstract

The tumor suppressor gene (TP^{53}) is crucial for DNA repair mechanism, apoptosis, and cell cycle regulation and progression. In human cancer, TP^{53} is mutated and highly polymorphic.[1] In the current case-control research investigation, we investigated TP^{53} gene SNPs, in exonic and intronic regions, as potential risk factors for colorectal cancer (CRC). This study comprised of 192 patients and 192 control. Obtained data illustrated that only the G allele;[1] rs1042522 (Pro72Arg (C G), demonstrated a statistically significant association, almost 1.5[1]-fold induction promotes the risk of CRC development in contrast to individuals with the C allele (OR = 1.5, $\chi 2$ = 7.28, p = 0.00696). The homozygous variant GG genotype of rs1042522 was also a significant risk factor to CRC development (OR= 2.1, $\chi 2$ = 6.41, p= 0.01136). SNP rs1042522 polymorphism established a considerably elevated odds of CRC among male patients aged 57 years and in patients' with tumors situated in colon region. In silico analysis exhibited that proline to arginine amino acid substitution affects the protein structure. Both rs1642785 and rs9894946 SNPs did not demonstrate any significant statistical association with CRC. In conclusion, this study confirmed that rs1042522 SNP within TP^{53} gene is correlated with possibility of developing CRC in the Saudi population. This finding highlights those polymorphisms within TP^{53} gene could act as a diagnostic indicator for CRC.

Keywords: TP^{53}, Genotyping, Cancer, Colorectal, SNP, Polymorphism

1. Introduction

Colorectal cancer (CRC) is deemed among major malignancies worldwide. It occurs as a result of accumulation of set of genetic and epigenetic modifications over time in different pathways that are proven to drive and transform the colonic epithelial cells into tumors (Houlston and Tomlinson 2001). It may take 10 to 15 years for the development and progression of carcinogenesis, which involves concurrent histological and nuclear changes (Fearon and Vogelstein 1990). Generally, variations in several biochemical pathways play vital roles in the development and transition from adenoma to carcinoma (Jesionek-Kupnicka, Braun et al. 2017). In colon cancer, approximately 90% of the cases are reported to have mutations in APC and in TP^{53} pathways (Michor, Iwasa et al. 2005). In this regard, the role of TP^{53} gene in suppression of tumor cannot be undermined. The human TP^{53} gene is positioned on chromosome 17 which has 11 exons and 10 introns (Lamb and Crawford 1986), and encodes TP^{53} protein. In over 50% of human cancers, TP^{53} undergoes mutation, while the remaining cases exhibit changes in its regulators or targets (Hu, Cao et al. 2021). In 1979, the TP^{53} protein was initially identified as an oncogene by different groups (Hernandez Borrero and El-Deiry 2021). Simultaneously, it was found to complex with the SV40 virus T antigen in cells undergoing 8-11 tumor transformation. Subsequently, other studies have identified interactions between this 53 kDa protein and adenovirus and human papillomavirus proteins (Werness, Levine et al. 1990). The "tumor antigen" is upregulated in tumor cells and seems to collaborate with other oncogenes like HRAS in converting primary cells into cultured cells (Miret, Molina et al. 2003). TP^{53} plays a crucial part in various biological processes, including DNA repair pathways, cell cycle regulation, and apoptosis (Levine and Oren 2009). TP^{53} is often altered in various cancers and it is a polymorphic gene. Many studies showed an enormous number of single nucleotide

polymorphisms (SNPs) in the exon, promoter, and intron regions of the TP^{53} gene. Some of these studies showed association between SNPs in TP^{53} and cancer (Whibley, Pharoah et al. 2009, Jesionek-Kupnicka, Braun et al. 2017, Sobieszkoda, Czech et al. 2017). This gene is critical to tumor progression and therapeutic response.[46] Therefore, the current study was intended to study the potential association of SNPs in TP^{53} gene with CRC in the Saudi population. We analyzed the association of TP^{53} (rs1042522, rs1642785, and rs9894946) polymorphism with CRC development among Saudi population.

[3 7]

2. Material and Methods

2.1. Patient Samples:

Samples from Saudi Arabia of CRC patients (n=192) and matched controls (n=192) were obtained from collaborators and clinicians according to the guidelines of 12/3352/IRB. [25] Patients visiting the Endoscopy Department at King Khalid University Hospital (KKUH) were examined by the oncologist alongside a routine examination. [49] There were no restrictions in patient group in terms of age and CRC stages. For genotyping studies, each patient donated blood volume of 5 ml. [18] Clinical and demographic traits such as tumor location, sex, age, and ethnicity, family history of cancer, lymph node status, and smoking habit were recorded for all the study participants (both cases and controls). [14] Informed consent statements were collected from all the study participants in accordance with the rules of the ethical review committee at King Saud Medical City, King Saud University.

2.2. [68] Nucleic Acid Isolation: [20]

Blood samples were utilized in the extraction process for Genomic DNA, by QIAamp DNA Blood Mini Kit (Qiagen, Valencia, CA, USA) as per manufacturer's guide. Briefly, 20µl protease was inserted in 200µl of blood samples in 1.5 ml tubes and mixed. [1] Next, AL buffer was incubated for 10 minutes at temperature of 56ºC. Mixed was then centrifugated and then transferred to spin columns. [1] Wash buffers 1 & 2 were inserted to the column, and centrifugated after each wash. [1] The elution was performed in 50µl AE buffer. [1] The yielded DNA was measured for volume and purity using the NanoDrop8000 spectrophotometer (Thermo Scientific).

2.3. Genotyping:

Both CRC and normal DNA samples were genotyped and amplified for TP^{53} SNPs by real-time polymerase chain reaction (PCR) using a TaqMan SNP genotyping assays as described (Alanazi,

Parine et al. 2013, Angelopoulou, Veletza et al. 2017, Ozdemirkiran, Nalbantoglu et al. 2017). Each well containing 20 ng of genomic DNA, 5.6 µL of TaqMan® Genotyping Master Mix (Applied Biosystems, Foster City, CA, USA), 0.2 µL of 40× TaqMan® Genotyping SNP Assay (Applied Biosystems). QuantStudio™ Real-Time PCR (Applied Biosystems) was used for each genotyping run with and an endpoint reaction reading. The setting of the PCR run are as follows; 1) pre-read stage for 30 seconds at 60°C temperature, 2) hold stage 10 minutes at 95°C, 3) 40 cycles at PCR stage 15 seconds for denaturation at 95°C and annealing for 1 minute at 60°C, and 4) post-read stage 30 seconds at 60°C.

2.4. Statistical Analysis:

The data analysis was conducted by calculating the allele frequencies. Genotype evaluated the differences between the samples, and the calculation was executed as per Pearson's goodness-of-fit chi-square. The allelic variations were calculated on the basis of wild type which was treated as a reference for the present investigation. Chi-square, odds ratios, p-values, and confidence intervals were computed by using IBM SPSS version 23. Haploview software was used to plot the Linkage disequilibrium (Barrett, Fry et al. 2004). In silico study done by using the online tool (https://www3.cmbi.umcn.nl/hope/input).

3. Results

The present study included 192 patients' samples diagnosed with CRC and 192 CRC patients, with earlier assent from every person.[7] Clinical and demographic details are presented in (Table 1). Genetic polymorphisms that were identified, i.e., rs1042522 (Pro72Arg (C G)) from the exonic region, rs1642785 (C G) in the intronic region, and rs9894946 (A G) in the intronic region, in TP53 gene variants, were examined in Saudi cohort diagnosed with CRC, to assess the risk of susceptibility to develop CRC.[79] The genotype distributions are demonstrated in Table 2. The genotype distributions for all the SNPs were in agreement with Hardy-Weinberg Equilibrium (HWE).[28] In the overall analysis, a statistically significant link was observed only with the G allele of rs1042522 (Pro72Arg (C G)), which showed a nearly 1.5-fold[28] increase in odds of CRC development in comparison to the individuals with the C allele (OR = 1.5, χ^2 = 7.28, p = 0.00696) (Table 1). The homozygous variant GG genotype of rs1042522 also had significant association with risk of CRC (OR= 2.1, χ^2 = 6.41, p= 0.01136).

The genotype frequencies of rs1642785 and rs9894946 did not show statistically significant associations in an overall comparison between CRC cases and controls (Table 2). Furthermore, we divided the samples into two subgroups stratified based on the median age of patients, i.e.,[32] below or above 57 years to study the influence of TP^{53} SNPs rs1042522, rs1642785 and rs9894946 on risk of CRC.[32] As shown in Table 3, a significant association was shown by the rs1042522 allele among CRC cases aged 57 years, but not in older patients. Both SNPs rs1642785 and rs9894946 did not display any association on age stratification among patients.

We also studied the effect of TP^{53} SNPs rs1042522, rs1642785, and rs9894946 on risk of CRC[36] development in subgroups stratified by sex (male and female).[32] As shown in Table 4, only rs1042522 polymorphism showed significant risk for developing CRC among male patients;

SNPs rs1642785 and rs9894946 not showing any association with CRC among patients stratified by the male gender. Among female, none of these SNPs confirmed statistical significance (Table 4).

Tumors location was also studied. The investigation into tumor location revealed that only variant rs1042522 exhibited a significantly higher risk of developing CRC in the colonic region for individuals with the homozygous GG allele ($\chi 2$: 7.00; CI: 1.24-4.66; p = 0.008), showing a 2.41-fold increase in risk. There was also an elevated risk association for the G allele ($\chi 2$: 7.78; CI: 1.15-2.29; p = 0.005) with a 1.63-fold increase in risk, but this association was not observed in the rectal region. There was no evidence to suggest that SNPs rs1642785 and rs9894946 were linked to tumors in the colon or rectal regions.

The pairwise linkage disequilibrium (LD) values (D' and r^2) are listed in Figure 1. For the SNPs, LD analysis revealed weak LD, forming one haplotype block, suggesting that haplotype evaluation may be beneficial. SNP rs9894946 showed disequilibrium (D'= 0.428, r^2= 0.168) in cases. The remaining two SNPs showed 0.1 D' and r^2 values in cases and controls.

[1 3]

4. Discussion

TP^{53} protein is a crucial component in maintaining genomic integrity which prevents the cells from oncogenic transformation.[2] Inactivation of TP^{53} is common occurrence in majority of the cancers. TP^{53} serves to regulate DNA repair, cell cycle, and cell development.[4] Any changes in TP^{53} function will abrupt these functions and culminate in loss of genome integrity.[5] Polymorphisms of the TP^{53} gene are widely established to take part in progression of CRC.[2] If the TP^{53} functioning is normal, it is a fundamental obstacle for carcinogenesis.[21] Few SNPs of TP^{53} coding region are strongly linked with the process of carcinogenesis.[21] They are commonplace in a large number of cancers, contributing to severe aberration in TP^{53} function.[13] Till now, approximately 200 SNPs are documented to be found commonly in TP^{53} which are expected to cause aberrations in TP^{53} functioning.[5] The purpose of current study was to perceive any associations of TP^{53} polymorphisms with development of CRC in Saudi Arabian population.[0] This study investigated the role of exonic and intronic SNPs (exonic rs1042522, Pro 72 Arg (C G), intronic rs1642785 (C G), and intronic rs9894946 (A G) of the TP^{53} gene as potential CRC risk factors in a case-control study involving 192 CRC cases and 192 matched normal control samples.[3]

Our study found a strong association between the GG genotype of SNP rs1042522 and an increased risk of CRC in the Saudi population.[3] Additionally, we observed that the minor allele (G) of the same SNP also independently contributes to a higher susceptibility to CRC (Table 2).[4] These results align with previous studies that have reported significant associations between the GG and/or G genotypes of rs1042522 and various cancer types (Ashton, Proietto et al. 2009, Ricks-Santi, Mason et al.[80] 2010, Tian, Dai et al. 2016). Findings from few other studies are in contrast with our results. For example, Dahabreh et al. (Dahabreh, Linardou et al. 2010) and

Kodal et al. (Kodal, Vedel-Krogh et al. 2017) reported no link between rs1042522 and cancer. In the current study, we sub-analyzed the possible association between three TP^{53} SNPs and CRC risk by age, sex, and tumor location. In our previous studies with various polymorphisms, we observed that susceptibility to CRC was significantly affected by age, sex, and tumor location (Alhadheq, Purusottapatnam Shaik et al. 2016, Semlali, Parine et al. 2017). We noticed a noteworthy association between the rs1042522 polymorphism (CG, GG genotypes, and minor allele G) and an increased risk of CRC in individuals aged 57 years. Surprisingly, SNP rs1642785 demonstrated a significant protective effect against CRC in patients 57 years. When comparing sexes, we observed that the rs1042522 SNP was linked to a higher risk of CRC in males in contrast to females. This finding aligns with a prior study that highlighted the influence of sex in susceptibility to CRC (Micheli, Ciampichini et al. 2009). Purim et al. reported that females are more protected against CRC development, with a lower related mortality rate when compared to males (Purim, Gordon et al. 2013). The observed phenomenon may be attributed to variances in physiology, diet, and hormones between males and females (Jacobs, Thompson et al. 2007). Moreover, SNP rs1042522 displayed a notable association with an increased risk of CRC specifically in patients with tumors situated in the colon region.

Various functional studies using genetically modified mice have consistently reported a notable link between TP^{53} gene polymorphisms and the vulnerability of patients to tumor progression. These studies have consistently shown that mice with a silenced mutation in one TP^{53} allele exhibit a lower incidence of tumors compared to mice with the mutation (Donehower, Harvey et al. 1992). Moreover, in a study conducted by Tina et al. (Tian, Dai et al. 2016) they emphasized that TP^{53} Pro72Arg polymorphism is extensively examined and significantly linked to cancer risk (Tian, Dai et al. 2016). In current research, we observed a significant correlation between

SNP rs1042522 (Pro72Arg) and CRC in our Saudi cohort. These findings are consistent with numerous previous studies investigating CRC and other cancer types (Dahabreh, Schmid et al. 2013). Consequently, it is plausible that this SNP may also be associated with the progression of CRC. The mutated amino acid is bigger in size than wild type. The mutation introduces a charge at this position; this can cause repulsion between the mutant residue and neighboring residues. The mutation might harm hydrophobic interactions with other molecules on protein surface (Figure 2). The wild-type residue is proline. Prolines are widely known as rigid and therefore induce a special backbone conformation which may be required at this position. The mutation can disturb this special conformation (Thomas, Kalita et al. 1999). The mutation might cause a loss of hydrophobic interactions with other molecules on the surface of the protein. Further, we have plotted LD plots for each individual SNP to sought their association with nearby SNPs. The LD plot demonstrates that, out of the three evaluated polymorphisms, none of the SNPs indicated r^2 0.80. As presented in Figure 3, the local LD plot was plotted by using the online SNP Annotation and Proxy Search tool (http://www.broadinstitute.org/mpg/snap/ldplot.php). The highest r^2 values for the SNPs studied were 0.749 for rs1042522, 0.749 for rs1642785, and 0.585 for rs9894946 (Figure 3). The regional association LD plot showed several positions near the rs1042522 SNP with high LD (r^2 = 0.749). SNP rs1042522 showed a close association with rs1642785 (r^2 = 0.749). The SNP rs1042522 exhibited a strong correlation with rs1642785 (r^2 = 0.749). In summary, our study indicates that the TP^{53} gene SNP rs1042522 (Pro72Arg) influences the susceptibility to CRC in Saudi population. However, to validate our findings, further investigation is needed in a larger cohort of individuals.

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