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A Study on Adenomatous Polyposis Coli (APC) and Myelocytomatosis (MYC) Gene Mutation in Fibroadenoma and Invasive Ductal AdenocarcinomaAkeredolu, F.F.*¹, Ekundina, V.O.¹ and Agbomhere, H.M.²

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<https://dx.doi.org/10.4314/sokjmls.v10i2.12>**Abstract**

Cancer is a multi-step process involving multiple cell types, and its prevention remains challenging in the world. Early diagnosis of breast cancer is one of the best approaches to prevent this disease. The pathogenesis and tumor drug-resistant mechanisms are revealed by discovering breast cancer stem cells, and many genes are found related to breast cancer. The purpose of this study was to assess APC and MYC gene mutation patterns in benign and malignant breast lesions in women who attended Federal Teaching Hospital. Ten (10) formalin fixed paraffin embedded (FFPE) tissue blocks which contained 5 fibroadenoma and 5 invasive ductal adenocarcinoma, were retrieved from the pathological archives of Federal Teaching Hospital Ido-Ekiti for this case control retrospective study. Nucleic acid amplification technique was used to carry out this study by using dellaporta DNA extraction protocol, then the samples will be purified, and polymerase chain reaction (PCR) technique will be used to amplify the DNA fragment. PCR includes denaturation, annealing, electrophoresis analysis and integrity. The amplified fragments were sequenced using a genetic analyzer from applied Biosystems using the manufacturers manual using the sequencing kit used was that of the big dye terminator v3.1 cycle sequencing kit. Bio-edited software and Mega 6 were used for all genetic analysis. The results were reported that in fibroadenoma in *apc* gene, single nucleotide polymorphism (SNPs) mutation recorded 100% transition and in invasive ductal adenocarcinoma it recorded 100% transition as well. In functional mutation in *apc* gene, fibroadenoma reported

50% silent and 50% missense while for invasive ductal adenocarcinoma it recorded 100% missense. The results reported in MYC gene show that in snps mutation for fibroadenoma, 50% transversion and 50% transition was discovered. In IDA, 18% transition, 29% InDel and 53% transversion were spotted. In functional mutation, fibroadenoma resulted to 50% silent and 50% missense while in IDA it was reported 71% silent and 29% missense. This study carried out demonstrated that missense mutation is more prevalent in both APC and MYC compared to fibroadenoma and invasive ductal adenocarcinoma singly. This research aided in finding out the correlation between APC and MYC gene which shows that one mutated gene can lead to the complication of another. The data generated from this research has highlighted the importance of carrying out further study in assessing both gene to understand their involvement in the etiology of carcinogenesis (it being the hallmark of cancer) which will In turn aid other research.

Keywords: Adenomatous Polyposis Coli (APC), Myelocytomatosis (MYC), Gene Mutation, Fibroadenoma and Invasive Ductal Adenocarcinoma

Introduction

Cancer is a multi-step process involving multiple cell types, and its prevention remains challenging in the world. Early diagnosis of breast cancer is one of the best approaches to prevent this disease. The pathogenesis and tumor drug-resistant mechanisms are revealed by discovering breast cancer stem cells, and many

genes are found related to breast cancer. (Incassati *et al.*, 2010). "Invasive ductal adenocarcinoma" refers to cancer that has broken through the wall of the milk duct and begun to invade the tissues of the breast. Over time, invasive ductal carcinoma can spread to the lymph nodes and possibly to other areas of the body. It is also malignant and cancerous (Xu *et al.*, 2003). Fibroadenoma are benign breast tumors characterized by an admixture of stromal and epithelial tissue. Fibroadenoma develop from the lobules. The glandular tissue and ducts grow over the lobule to form a solid lump (Jones, 2003). Adenomatous polyposis coli (APC) gene is a tumor suppressor gene responsible for the production of adenomatous polyposis coli (APC), a large multifunction tumor-suppressing protein which acts as a "gatekeeper" to prevent development of tumors (Zheng *et al.*, 2013). Multiple mechanisms are involved in Myelocytomatosis oncogene (MYC) deregulation in breast cancer, including gene amplification, transcriptional regulation, and mRNA and protein stabilization, which correlate with loss of tumor suppressors and activation of oncogenic pathways (Jinhua *et al.*, 2003).

Materials and Methods

Sample Collection and DNA Extraction

Ten processed tissue block from the pathology archive in the department of histopathology, federal teaching hospital, Ido-ekiti, Ekiti state. Total number of two cases were confirmed, one was a fibroadenoma tissue block and the other one was an invasive ductal adenocarcinoma tissue block. It was sectioned using a microtome to cut out thin sections and it was dewaxed using xylene. Three (6) different methods were used when conducting this research: DNA extraction, PCR (polymerase chain reaction), isolation of gene of interest, integrity test, purification, DNA sequencing.

DNA Extraction

It involves the removal of DNA from the cell. Procedure: DNA was extracted by using a modified Dellaporta DNA extraction protocol. Briefly, samples on slides were neatly scrapped into a sterile mortar containing 500mls Dellaporta extraction buffer (100 mM Tris pH 8, 51 ml EDTA pH 8, 500 mM NaCl, 10 mM mercaptoethanol) and grinded with a sterile

pestle. Mix was collected in sterile Eppendorf tube and 33 μ l of 20% SDS was then added, this was followed by brief vortexing and incubated at 650 C for 10 minutes. At room temperature, 160 μ l of 5 M potassium acetate was then added vortexed then 600 μ l Phenol Chloroform Isoamyl Alcohol was added in the ration 25:24:1. The mix was then vortex and centrifuged at 10000 g for 10 minutes. Supernatant where collected in another Eppendorf tube and 400 μ l of cold Isopropanol was added mixed gently and kept at -20degreesS for 60 minutes. Centrifugation was at 13000g for 10 minutes to precipitate DNA after which supernatant was gently decanted and ensured that the pellet was not disturbed. DNA was then washed with 500 μ l of 70 % ethanol by centrifuging at 10000g for 10 minutes. Ethanol was decanted and DNA air-dried at room temperature until no trace of ethanol was seen in the tube. Pellet was then re-suspended in 50 μ l of Tris EDTA buffer to preserve and suspend the DNA. Breaking of the cells open to release the DNA (cell lysis)

The cells in the sample would be separated from each other by a physical means such as grinding, and it would be kept in a solution containing salt. The positively charged sodium ions help protect the negatively charged phosphate groups that run along the backbone of the DNA. Separation of DNA from proteins and other cellular debris: A protease is added to degrade DNA associated proteins and other cellular components. it is being removed by filtering the sample. DNA precipitation with alcohol: Ethanol would be added to the DNA sample. It would be stirred gently with a sterile pipette, a precipitate becomes visible and would be spooled out. Purification of DNA. The DNA sample would be purified by suspending it in an alkaline buffer. DNA confirmation: The use of a spectrophotometer would be used to take the optical readings for determining the concentration, quality and purity of the DNA.

Polymerase Chain Reaction Method

This technique helps to amplify the DNA fragments. The PCR method involve 3 steps; Denaturation, annealing, extension, electrophoresis analysis In denaturation the sample would be denatured using a thermal

cycler, whereby it would be heated under the temperature of (94 degrees). It breaks the hydrogen bond and separates the DNA into single strands. The sample would be cooled down to a temperature between 50 to 60 degrees (Annealing). After the annealing method, a new DNA molecule would be formed. It would be repeated 30-40 times using a thermocycler which helps in the heating and cooling process. Once all the processes are done, the resulting amplified segments are generated to compare to other nucleotide segments from a known source. It would be kept in a separating gel (Parmer, 2021). Isolation of gene of interest.

Integrity

The integrity of the amplified gene fragment was checked on a 1.5% Agarose gel run to confirm amplification. The buffer (1XTAE buffer) was prepared and subsequently used to prepare 1.5% agarose gel. The suspension was boiled in a microwave for 5 minutes. The molten agarose was allowed to cool to 60°C and stained with 3µl of 0.5 g/ml ethidium bromide (which absorbs invisible UV light and transmits the energy as visible orange light). A comb was inserted into the slots of the casting tray, and the molten agarose was poured into the tray. The gel was allowed to solidify for 20 minutes to form the wells. The 1XTAE buffer was poured into the gel tank to barely submerge the gel. Two microliter (2 l) of 10X blue gel loading dye (which gives color and density to the samples to make it easy to load into the wells and monitor the progress of the gel) was added to 4µl of each PCR product and loaded into the wells after the 100bp DNA ladder was loaded into well 1. The gel was electrophoresed at 120V for 45 minutes visualized by ultraviolet trans-illumination and

photographed. The sizes of the PCR products were estimated by comparison with the mobility of a 100bp molecular weight ladder that was run alongside experimental samples in the gel.

Purification of Amplified Product

After gel integrity, the amplified fragments were ethanol purified in order to remove the PCR reagents. Briefly, 7.6 µl of Na acetate 3M and 240 µl of 95% ethanol were added to each about 40µl PCR amplified product in a new sterile. Five (5) µl tube Eppendorf, mix thoroughly by vortexing and keep at -20°C for at least 30 min. Centrifugation for 10 min at 13000 g and 4°C followed by removal of supernatant (invert tube on trash once) after which the pellet were washed by adding 150 µl of 70% ethanol and mix then centrifuge for 15 min at 7500 g and 4°C. Again, remove all supernatants (invert tube on trash) and invert tube on paper tissue and let it dry in the fume hood at room temperature for 10-15 min. then resuspend with 20 µl of sterile distilled water and kept in -20°C prior to sequencing. The purified fragment was checked on a 1.5% Agarose gel run on a voltage of 110V for about 1hr as previous, to confirm the presence of the purified product and quantified using a Nano drop of model 2000 from thermo scientific.

DNA Sequencing

The amplified fragments were sequenced using a Genetic Analyzer 3130xl sequencer from Applied Biosystems using manufacturers' manual while the sequencing kit used was that of Big Dye terminator v3.1 cycle sequencing kit. Bio- Edit software and MEGA 6 were used for all genetic analysis.

Result

Summary table showing the effect of mutation along APC Gene

GENE TYPE	SPECIMEN	MUTATION TYPE	DESCRIPTION	LOCATION/FREQUENCY	MUTATION TYPE2
APC		INDEL			
APC		TRANSVERSION			
APC	IDA	PURINE TO PURINE TRANSITION	A:G	162(7:3)	MISSENSE MUTATION CHANGING ASPARAGINE TO SERINE
APC	IDA	PURINE TO PURINE TRANSITION	A:G	162(8:2)	MISSENSE MUTATION CHANGING ASPARAGINE TO SERINE
APC	IDA	PURINE TO PURINE TRANSITION	A:G	162(9:1)	MISSENSE MUTATION CHANGING ASPARAGINE TO SERINE
APC	IDA	PURINE TO PURINE TRANSITION	G:A	573(7:3)	MISSENSE MUTATION CHANGING ALANINE TO THREONINE
APC	IDA	PURINE TO PURINE TRANSITION	G:A	573(8:2)	MISSENSE MUTATION CHANGING ALANINE TO THREONINE
APC	IDA	PURINE TO PURINE TRANSITION	G:A	573(9:1)	MISSENSE MUTATION CHANGING ALANINE TO THREONINE
APC	FA	PYRIMIDINE TO PYRIMIDINE TRANSITION	T:C	625(2:8)	SILENT MUTATION BOTH CODING FOR TYROSINE
APC	FA	PYRIMIDINE TO PYRIMIDINE TRANSITION	T:C	625(3:7)	SILENT MUTATION BOTH CODING FOR TYROSINE
APC	FA	PYRIMIDINE TO PYRIMIDINE TRANSITION	T:C	625(4:6)	SILENT MUTATION BOTH CODING FOR TYROSINE
APC	IDA	PURINE TO PURINE TRANSITION	A:G	765(9:1)	MISSENSE MUTATION CHANGING GLUTAMATE TO GLYCINE
APC	FA	PYRIMIDINE TO PYRIMIDINE TRANSITION	C:T	902(3:7)	MISSENSE MUTATION CHANGING PROLINE TO SERINE
APC	FA	PYRIMIDINE TO PYRIMIDINE TRANSITION	C:T	902(4:6)	MISSENSE MUTATION CHANGING PROLINE TO SERINE
APC	FA	PYRIMIDINE TO PYRIMIDINE TRANSITION	C:T	902(5:5)	MISSENSE MUTATION CHANGING PROLINE TO SERINE
APC	IDA	PYRIMIDINE TO PYRIMIDINE TRANSITION	C:T	902(6:4)	MISSENSE MUTATION CHANGING PROLINE TO SERINE
APC	IDA	PYRIMIDINE TO PYRIMIDINE TRANSITION	C:T	902(7:3)	MISSENSE MUTATION CHANGING PROLINE TO SERINE
APC	IDA	PYRIMIDINE TO PYRIMIDINE TRANSITION	C:T	902(8:2)	MISSENSE MUTATION CHANGING PROLINE TO SERINE
APC	IDA	PYRIMIDINE TO PYRIMIDINE TRANSITION	C:T	902(9:1)	MISSENSE MUTATION CHANGING PROLINE TO SERINE
APC	IDA	PYRIMIDINE TO PYRIMIDINE TRANSITION	C:T	902(10:0)	MISSENSE MUTATION CHANGING PROLINE TO SERINE

Summary Table Showing the Effects of Mutation Along MYC Gene

GENE TYPE	SPECIMEN	MUTATION TYPE	DESCRIPTION	LOCATION/FREQUENCY	MUTATION TYPE2
MYC	IDA	INDEL	C	171(9:1)	INSERTION OF ASPARAGINE
MYC	IDA	INDEL	T	231(9:1)	DELETION OF CYSTEINE
MYC	IDA	INDEL	G	609(9:1)	INSERTION OF ALANINE
MYC	IDA	INDEL	C	649(9:1)	DELETION OF ARGININE
MYC	IDA	INDEL	A	659(9:1)	INSERTION OF THREONINE
MYC	IDA	TRANSVERSION	T:A	229(9:1)	MISSENSE MUTATION CHANGING CYSTEINE TO SERINE
MYC	IDA	TRANSVERSION	A:T	498(9:1)	SILENT MUTATION BOTH CODING FOR ARGININE
MYC	IDA	TRANSVERSION	C:G	401(9:1)	MISSENSE MUTATION CHANGING ALANINE TO GLYCINE
MYC	IDA	TRANSVERSION	G:C	549(9:1)	SILENT MUTATION BOTH CODING FOR ALANINE
MYC	FA	TRANSVERSION	G:C	767(4:6)	MISSENSE MUTATION CHANGING GLUTAMIC ACID TO GLUTAMINE
MYC	FA	TRANSVERSION	C:G	463(4:6)	SILENT MUTATION BOTH CODING FOR LEUCINE
MYC	IDA	TRANSVERSION	C:G	463(5:5)	SILENT MUTATION BOTH CODING FOR LEUCINE
MYC	IDA	TRANSVERSION	C:G	463(6:4)	SILENT MUTATION BOTH CODING FOR LEUCINE
MYC	IDA	TRANSVERSION	C:G	463(7:3)	SILENT MUTATION BOTH CODING FOR LEUCINE
MYC	IDA	TRANSVERSION	C:G	463(9:1)	SILENT MUTATION BOTH CODING FOR LEUCINE
MYC	IDA	TRANSVERSION	C:G	463(10:0)	SILENT MUTATION BOTH CODING FOR LEUCINE
MYC	IDA	TRANSITION	G:A	589(9:1)	MISSENSE MUTATION CHANGING ALANINE TO THREONINE
MYC	IDA	TRANSITION	G:A	733(9:1)	MISSENSE MUTATION CHANGING ALANINE TO THREONINE
MYC	IDA	TRANSITION	C:T	386(9:1)	MISSENSE MUTATION CHANGING ALANINE TO VALINE

A pie chart showing the APC single nucleotide polymorphism mutation in FA and IDA

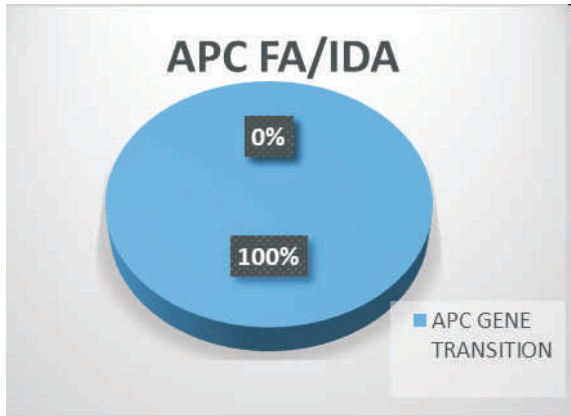


Figure 1: A pie chart showing the APC single nucleotide polymorphism mutation in FA and IDA which showed 100% transition

A pie chart showing the comparison between fibroadenoma and invasive ductal adenocarcinoma mutation frequency within APC gene

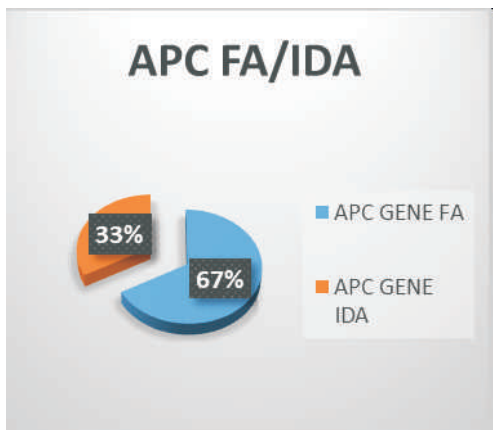


Figure 3: A pie chart showed the comparison between fibroadenoma and invasive ductal adenocarcinoma mutation frequency within

A pie chart showing the APC functional mutation in FA and IDA

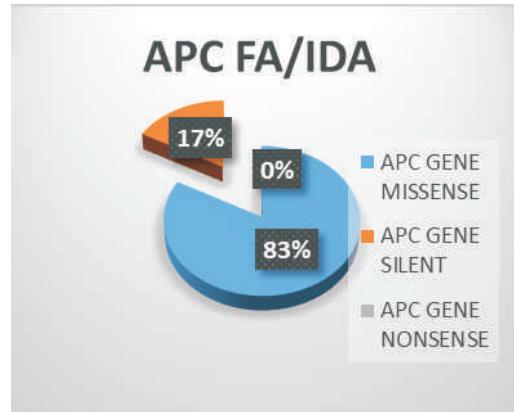


Figure 2: A pie chart showing the APC functional mutation in FA and IDA which shows that 17% silent and 83% missense mutation.

A Pie chart showing the MYC functional mutation frequency in FA and IDA

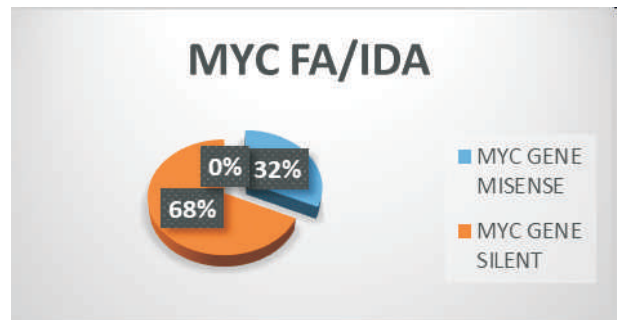


Figure 5: Pie chart showing the MYC functional mutation frequency in FA and IDA which shows 32% missense mutation and 68% silent mutation.

APC gene which showed mutation in 33% in IDA and 67% in FA.

A Pie chart showing the MYC single nucleotide polymorphism mutation frequency in FA AND IDA.

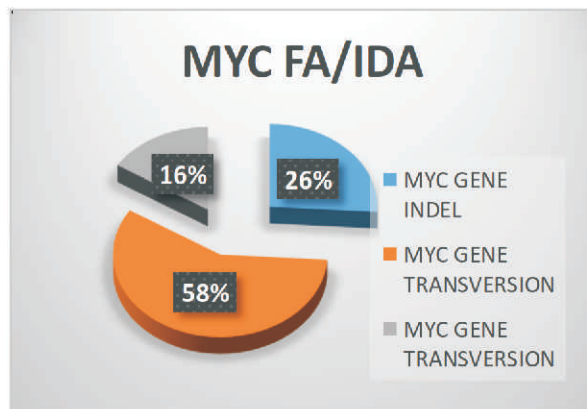


Figure 4: This Pie chart showed the MYC single nucleotide polymorphism mutation frequency in FA AND IDA showing 16% transition, 26% InDel and 58% transversion.

A pie chart showing the comparison between FA and IDA frequency within MYC gene

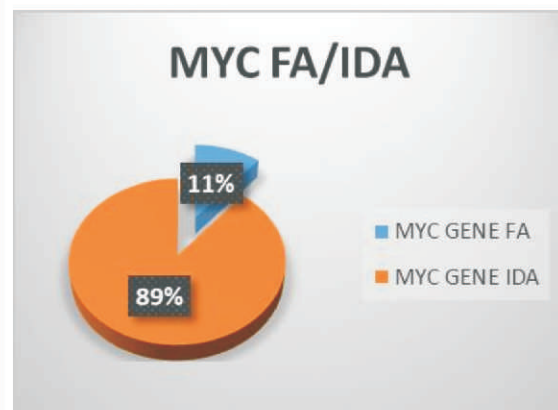


Figure 6: pie chart showing the comparison between FA and IDA frequency within MYC gene which shows

Discussion

Understanding carcinogenesis has been widely studied and serves as an efficient mode of diagnosing mutations that lead to progression of benign lesion to malignant lesion. Breast cancer is the leading cause of cancer deaths among women. The development of breast cancer is a multi-step process involving multiple cell types, and its prevention remains challenging in the world. Early diagnosis of breast cancer is one of the best approaches to prevent this disease. The pathogenesis and tumor drug-resistant mechanisms are revealed by discovering breast cancer stem cells, and many genes are found related to breast cancer (Incassati *et al.*, 2010). Ten (10) formalin fixed paraffin tissue sections were used for this study. Five (5) cases of fibroadenoma and 5 cases of invasive ductal carcinoma was analyzed and reported. In APC gene, fibroadenoma recorded 100% transition SNPs gene mutation. This agrees with (Faranak *et al.*, 2021) clinical laboratory analysis which demonstrated the nature and effect of APC gene

mutation in FAP (familial adenomatous polyposis) tumorigenesis. Screening 59 FAP Iranian patients in 10 families performing PCR and the direct sequencing of the entire coding exons of the APC gene. This study reported that heterozygous and homozygous nucleotide variations were identified, they included 2 missense, 4 nonsense mutations and 2 nucleotide deletion. In addition, 3 novel heterozygous nonsense mutation were found in exons 10, 14 and 15 of the gene.

This is at variance with (Sousan *et al.*, 2020) which demonstrated a cross-sectional case study of APC gene rs41115 polymorphism is associated with survival in Iranian colorectal cancer patients, polymorphism was observed in all patients; 35 patients had AG genotype, and 22 patients had AA genotype. Also, a missense mutation and 2 deletions were found. Pearson's correlation test showed a significant correlation between the stage of the disease and an anatomical subsite of the tumor polymorphism.

Overall comparison of survival function in the different genotypes of the APC gene showed significant difference between groups.

Also, in *apc* gene, invasive ductal adenocarcinoma also recorded 100% transition. This agrees with (Ghatak *et al.*, 2017) which was used to investigate the role of APC tumor suppressor gene in gastric cancer. Somatic mutations in the Exons 14 and 15 of APC gene from 40 diffuse type gastric cancer samples. Rabbit polyclonal anti-APC antibody was used, which detects the wild-type APC protein and was recommended for detection of the respective protein in human tissues. Cell cycle analysis was done from tumor and adjacent normal tissue. The result showed that APC immunoreactivity showed positive expression of the protein in stages I, II, III and negative expression in Stages III and IV. Two novel deleterious variations (g.127576C>?A, g.127583C>?T) in exon 14 sequence were found to generate stop codon (Y622* and Q625*) in the tumor samples. Due to the generation of stop codon, the APC protein might be truncated, and all the regulatory features could be lost which has led to the down-regulation of protein expression. Our results indicate that aneuploidy might occur due to codon 622 and 625 APC-driven gastric tumorigenesis, in agreement with our cell cycle analysis. The APC gene function in mitosis and chromosomal stability might be lost and G1 might be arrested with high quantity of DNA in the S phase. Six missense somatic mutations in tumor samples were detected in exon 15 A-B, two of which showed pathological and disease-causing effects based on SIFT, Polyphen2 and SNPs & GO score and were not previously reported in the literature or the public mutation databases. This is in variance with (Faranak *et al.*, 2021) which demonstrated a mutational screening through comprehensive bioinformatics analysis to detect novel germline mutations in the detection of novel germline mutations in the APC gene in patients with familial adenomatous polyposis coli. 59 FAP Iranian patients in 10 families was performed by polymerase chain reactions and the direct sequencing of the entire coding exons of the APC gene. To do linkage haplotype analysis and multiplex PCR base microsatellite examination,

six short tandem repeat loci were selected in this gene. To evaluate and predict the potentially deleterious effects, comprehensive bioinformatics pathogenicity assays can be used. The result showed that 12 germline heterozygous and homozygous nucleotide variations were identified. They included 2 missense and 4 nonsense mutations which would lead to truncated and nonfunctional protein products, four synonymous or silent variations and 2 nucleotide deletions of 1 to 5 bp or frameshift mutations. In addition, three novel heterozygous nonsense mutations were found in exons 10, 14 and 15 of the gene. In *myc* gene mutation fibroadenoma showed that there was 50% transversion and 50% transition this is in agreement with (Xu-Monette *et al.*, 2016) which was used to investigate the Clinical and Biologic Significance of MYC Genetic Mutations in De Novo Diffuse Large B-cell Lymphoma which was used to identified MYC mutations in 750 patients with DLBCL using Sanger sequencing and evaluated the prognostic significance in 602 R-CHOP-treated patients. The result showed that the frequency of MYC mutations was 33.3% at the DNA level (mutations in either the coding sequence or the untranslated regions) and 16.1% at the protein level (nonsynonymous mutations). Most of the nonsynonymous mutations correlated with better survival outcomes; in contrast, T58 and F138 mutations (which were associated with MYC rearrangements), as well as several mutations occurred at the 3' untranslated region, correlated with significantly worse survival outcomes. However, these mutations occurred infrequently (only in approximately 2% of DLBCL). A germline SNP encoding the Myc-N11S variant (observed in 6.5% of the study cohort) was associated with significantly better patient survival and resulted in reduced tumorigenicity in mouse xenografts. Which is at variance to (Iba *et al.*, 2004) who demonstrated the expression of the *c-myc* gene as a predictor of chemotherapy response and a prognostic factor in patients with ovarian cancer. This study includes 101 consecutive patients with stage Ic to IV epithelial ovarian cancer who underwent primary surgery followed by platinum-based chemotherapy. Immunohistochemical studies were performed to detect Ki-67 and ARF proteins. Apoptotic

cells were identified by the terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate biotin nick-end labeling method. The mutation of the p53 gene was screened by polymerase chain reaction (PCR)-single strand conformation polymorphism analysis and confirmed by direct sequencing. mRNA expression of c-myc was determined by means of reverse transcription-PCR. Apoptotic index (AI) and ARF labeling index (LI) were significantly increased and Ki-67 LI was decreased after chemotherapy in patients from whom specimens could be obtained before and after chemotherapy. AI, ARF LI, and Ki-67 LI were not related to p53 gene status. A significant correlation between the expressions of c-myc and ARF LI was observed. Of 38 patients with measurable lesion, 23 (60.5%) responded to chemotherapy and 15 (39.5%) did not. Tumors with the wild-type p53 gene responded significantly better to chemotherapy than did tumors with the mutation. Responders showed a higher expression of c-myc than nonresponders (468.76 vs. 187.68). The receiver operating characteristic (ROC) curve according to chemo response demonstrated that the cut-off value of c-myc expression was 200. Patients with c-myc expression of more than 200 had a better 5-year survival rate (69.8% vs. 43.5%; 101 patients). Multivariate analysis revealed that c-myc expression was an independent prognostic factor. Our results suggest that the expression of c-myc gene is related to chemo response and might be a useful prognostic factor in patients with epithelial ovarian cancer.

Conclusion

This study carried out demonstrated that missense mutation is more prevalent in both APC and MYC compared to fibroadenoma and invasive ductal adenocarcinoma singly. This research aided in finding out the correlation between APC and MYC gene which shows that one mutated gene can lead to the complication of another. The data generated from this research has highlighted the importance of carrying out further study in assessing both gene to understand their involvement in the etiology of carcinogenesis (it being the hallmark of cancer) which will in turn aid other researches.

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