Association SNP (Rs10889677) In Mirnas Let-7f and Let-7e Binding Site of IL23R Gene with Colorectal Cancer

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Abstract

The current study aims to Associate SNP (rs10889677) in miRNAs Let-7f and Let-7e binding site of IL23R gene with colorectal cancer in some Iraqi cases, The result of DNA- sequencing of the desired SNPs rs10889677 C >A, shown, the percentage of deletion mutation in patient was 33.33% while in control group 7.6% (p 0.014), deletion mutation was higher in male 20.8% than female12.5%, the percentage of deletion mutation was 29.16% in Adenocarcinoma, 4.16% in Mucinous adenocarcinoma, The distribution of deletion mutation in cancer grade, in the well differentiated the percentage of deletion mutation was 16.66% , in the midrate differentiated was 12.5% , in the Poor differentiated was 2.08%, The metastases of lymph node the deletion mutation, in the N0 was 16.66%, in the N1 8.33% , in the N2 was 2.08%, in the N2b was 6.25%, belong to cancer stage, the highest percentage in III (12.5%), in the I stage was (8.3%) , in the IIb (6.25%) and in the IIA stage was (4.16%) while no deletion mutation appeared in other stages include (II, IV, IIIC and IIC). According to metastasis; in the Mx stages the deletion mutation was (4.16%) whlile in the M1 the deletion mutation was (31.25%) , The result of genotyping shows three genotyping homozygotes (CC) and (AA), heterozygote (AC) the most common genotyping in patient AC with (18) in patient and (16) in control group, the second common genotyping in patient group was (CC) with frequency (9) and (2) in control group, the last genotyping was AA was more frequent in control group (6) than patient group (5), all of them were non- significant differences. The genotyping distribution shows no significant differences in all sub types, the AC was more frequent in Adenocarcinoma (9) in Mucinous adeno carcinoma AC was more frequent (6) , the AC was most common in the stages well differentiated was (11) while in the Moderate differentiated (6) and in the high grad (1) the Metastases of Lymph node showed AC was higher in N0 (9), in N2 was (4) and (2) in both N1 and N2a, the frequencies of CC in N0 and N1 was (3), in N2, N1b and N2b was (1) and absence in N2a. The AC was more frequency (16) in Metastases stages Mx while in M1 was (2), the current study conclusion that there was robust association of deletion mutation in this region but didn't association of rs10889677 variation with colorectal cancer characterization.

Keywords: SNP (rs10889677), miRNAs Let-7f, Let-7e binding site, IL23R gene colorectal cancer

1. Introduction

The current study aims to detect the two Single nucleotide polymorphism rs10889677 in miRNA Let-7e and Let-7f binding site, in some Iraqi cases, The let-7 family members are encoded by 12 chromosomal loci in humans (let-7a-1, -2, -3; let-7b; let-7c; let-7d; let-7e; let-7f-1, -2; let-7g; let-7i; mir98). During the differentiation of embryonic cells, human let 7 is increased (Bar *et al.*, 2008), although it is mostly unknown what functions it performs in healthy physiology. With a few notable exceptions, it has been discovered that members of the human let-7 family are down regulated in a number of malignancies; restoration of normal expression stops carcinogenesis (Inamura *et al.*, 2007; Johnson *et al.*, 2007; Takamizawa *et al.*, 2004; Kumar *et al.*, 2008). This study suggests that let-7 may someday be employed as a next-generation cancer therapy because let-7 functions as a tumor suppressor as well as a regulator of terminal differentiation and death. However, the actual mechanism of let-7 deregulation and its part in carcinogenesis remain poorly understood, which makes it difficult to use this miRNA successfully in cancer therapy, thus it choses in current study.

2. Methodology

The Current work is design as a case control study including (49 colorectal cancer cases consist of 31 women and 17 men, with age 56.17±1.98 years) and 30 healthy individuals). Imbedded tissues samples were collected from different pathology labs, that diagnosed by specialist pathologist physician. DNA extraction performed according to manufacture leaflet of FavorPrep™, then SNP (rs10889677) were detected by PCR-sequencing using f-CATGTTTTCATTTCCCTTGGA, and r-TGTGCCTGTATGTGTGACCA. Then PCR products were sequenced by macrogene company, data was

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analyzed to determined SNP and statistical analysis implemented using X2, odd ration, confidence intervals 95% at p value <0.05.

Results and discussion

The results of rs10889677 SNPs genotyping showed that the Polymerase chain reaction product about (249bp) for both cancer patients and control group as shown in Figure (1).

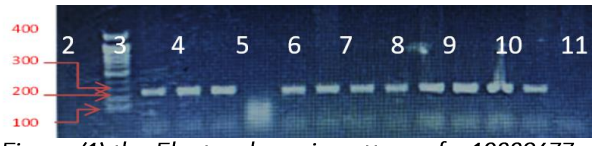

Figure (1) the Electrophoresis pattern of rs10889677 amplification in study groups, M DNA ladder (100-1000bp), lanes 1-6 amplification target SNP in patients, lanes 7-13 amplification target SNP in control group, samples 4 and 13 referred to deletion mutation in study groups. Amplification products 249 bp.

The miRNA let 7 plays a vital role in tumor suppression in many cancers, including esophageal squamous cell carcinoma, lung cancer and prostate cancer (Liu et al., 2008; Wagner et al., 2014; Yang et al., 2015). In addition, let-7 is also associated with poor prognosis in HCC patients (Xie et al., 2018). Let-7 has a number of subtypes (a, b, c, d, e, f, and g). Let 7 is a tumor suppressor that targets many oncogenes, according to a wealth of evidence, and its level is highly correlated with enhanced tumorigenicity and a poor prognosis for patients (Yang et al., 2015; Ma et al., 2015).

The result of DNA- sequencing of the desired SNPs rs10889677 C >A, shown deletion mutation of wide region in patient with colon cancer as compared with control group,

It has become clear in recent years that variations in the expression of numerous miRNAs were connected to the manifestation of the cancer phenotype through regulation of essential cellular processes such proliferation, differentiation, migration, angiogenesis, and apoptosis (Ha and Kim 2014). Because of this, miRNAs make interesting targets for cutting-edge treatment strategies. Additionally, miRNAs are a viable biomarker for assessing tumor initiation, progression, and metastasis due to their production into extracellular fluids.

the result of analyses of SNPs rs10889677 C >A showed three genotyping homozygotes CC and AA, heterozygote AC in both study group Figure (2).

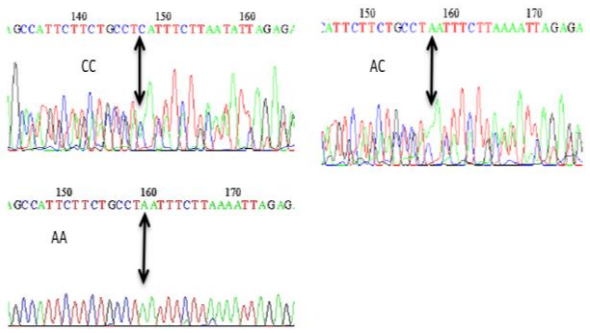

Figure (2) the histograms of rs10889677 sequences in study groups (homozygotes CC and AA, heterozygote AC)

The unregulated expression of miRNAs in malignancies may be explained by the existence of a single nucleotide polymorphism (SNP) in the miRNA genes. Even if the polymorphism has no effect on the mature miRNA's level of expression, it could still have an impact on how the miRNA regulates the activity of its target genes. The pri-miRNA and pre-miRNA processing levels, as well as the miRNA-mRNA interactions levels, can all be affected by the miRNA genes polymorphisms. The first level of modification is at the transcription level of the primary transcript, where SNPs in miRNA biogenesis genes and pri-miRNA SNPs are found. The second level of modification is at the pri-miRNA and pre-miRNA processing levels (Slaby et al., 2012; Park et al., 2020).

SNPs may be found in a variety of crucial areas, such as the miRNA genes' promoter regions, where they have an impact on the expression of mature miRNAs (Kim et al., 2019) or in other crucial areas like the "seed" region, which is a conserved sequence that is primarily located around positions 2-7 from the miRNA 5'-end and is crucial for the binding of the miRNA to the mRNA (Moszyńska et al., 2017). SNPs in this region may change how complementarity between target genes and miRNAs works, which could destabilize several biological pathways. (Vodicka, et al., 2016).

SNPs in the miRNA gene area may affect miRNA production and maturation, affecting the function, stability, and targeting of mature miRNAs (Shen et al., 2008). Moreover, CRC incidence, prognosis, and treatment responsiveness may be impacted by SNPs in miRNA genes or miRNA machinery (Vodicka, et al., 2016) Mullany et al. (2016) hypothesized, however, that SNPs also affect cancer, albeit not via miRNAs, and additional mechanisms other from SNPs may regulate mature miRNA levels.

The deletion mutation was observed in both patients and control group, the percentage of deletion mutation in patient was 33.33% while in control group 7.6%, the remain sample that observed the normal gene without deletion was 66.66% in patient and 92.3% in control group, there is statistically differences at p-value 0.014 between normal and deletion mutation in the study group. Figure (3)

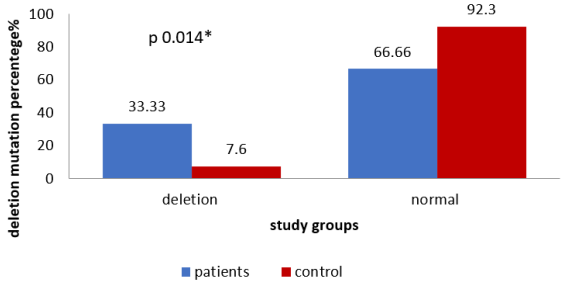

Figure (3) the percentage of deletion mutation (rs10889677) in study group

(X2 square, p <0.05).

The result of DNA sequencing analysis shown that the most common type of mutation is observed in

rs10889677 was deletion mutation and the normal gene (without deletion in the gene), according to the gender deletion mutation was higher in male 20.8% than female12.5%, while the normal also higher in male 43.75% than female 22.91%, and there are not significantly differences in the study group, Figure (4)

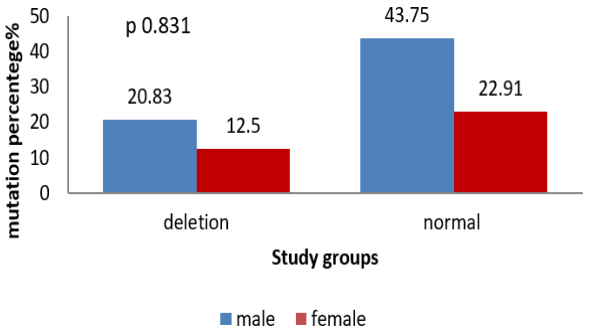

Figure (4) the percentage of deletion mutation (rs10889677) in study group according to sex (X2 square, p <0.05).

Numerous crucial mammalian genes, such as those controlling cell cycle progression, apoptosis, and tumor biogenesis inhibitors, are subject to posttranscriptional regulation through interaction with microRNAs (miRNAs), which bind to their specific recognition elements known as seed sequences at 3'-untranslated region (UTR) of mRNAs (Bhaumik et al., 2014; Landi et al., 2008). Each mRNA has several conserved seed sequences for miRNAs, and any SNPs could disrupt the thermodynamic properties of the miRNA-mRNA hybridization site (Ahangari et al., 2014; Liu et al., 2012; Fang et al., 2011). In fact, a growing body of research has indicated that miRSNPs represent a novel class of interesting polymorphism variations that are worth studying and may open up new fields of study in cancer biology and clinical oncology (Mishra et al., 2008; Mosallayi et al., 2017).

Additionally, it has been proposed that miRSNPs could be used as practical biomarkers for the investigation of cancer disease development, patient prognosis, and therapy effectiveness (Mishra et al., 2009; Salzman et al., 2013). It is generally known that inflammation and tumor formation, particularly in CRC, are related. Cytokines and chemokines, which are frequently produced by cells like macrophages, B and T lymphocytes that are drawn to the tumor microenvironment, induce inflammation (Terzi ´c et al., 2010; Tang et al., 2014)

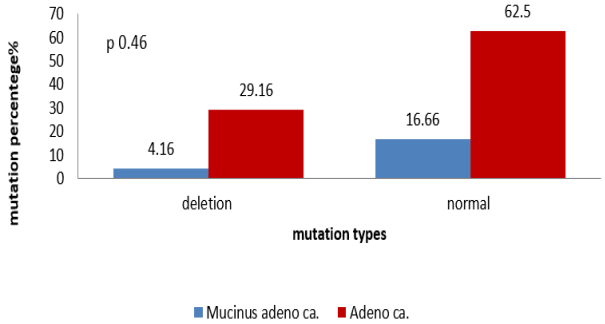

Figure (5) the deletion mutation percentage of (rs10889677) in colon cancer subtype patients

The two types of colon cancer were investigated in this study the Mucinous adenocarcinoma and Adenocarcinoma, according to the result of sequencing analysis the percentage of deletion mutation was 29.16% in Adenocarcinoma, 4.16% in Mucinous adenocarcinoma, while in the normal the percentage was 62.55, 16.66% in both Adenocarcinoma and Mucinous adenocarcinoma, Respectively and there were no significant differences among two type, Figure (5).

The result of distribution of deletion mutation in cancer grade, in the well differentiated the percentage of normal (without deletion) was 37.5% , while the percentage of deletion mutation was 16.66% , in the midrate differentiated also the higher percentage was normal 27.08% while the percentage of deletion mutation was 12.5% , in the Poor differentiated only deletion mutation appeared with percentage 2.08% , in the high grad of colon cancer the normal only appeared with 2.08% , and there were no significant differences observed among grade of colon cancer , as shown in (Figure 6), by comparing the percentage of deletion mutation in all grade of colon cancer the percentage of deletion mutation from highest to the lost (16.66% , 12.55 , 2.08% and 0), well differentiated , midrate differentiated, poor differentiated and high grade respectively .

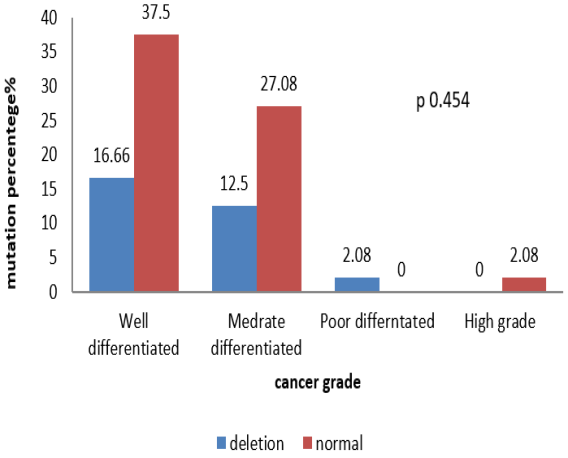

Figure (6) the deletion mutation percentage of (rs10889677) in colon cancer patients according to cancer grade

The metastases of lymph node the deletion mutation appeared in all grade of lymph node metastases, in the N0 the percentage of deletion mutation e\was 16.66% and 33.33% is normal, in the N1 8.33% was deletion mutation and 12.5% was normal, in the N2 2.08% was deletion and 10.41% was normal, N1b no deletion mutation observed and 4.16% normal, in the N2b the deletion mutation was 6.25% and 2.08% was normal, in the N2a no deletion mutation and 4.16% was normal , by compare the percentage of deletion mutation in lymph node the highest percentage was in N0 while deletion mutation not observed in both N1b and N2a , and there is significantly differences among study group p-value (p≥0.050) Figure (7) .

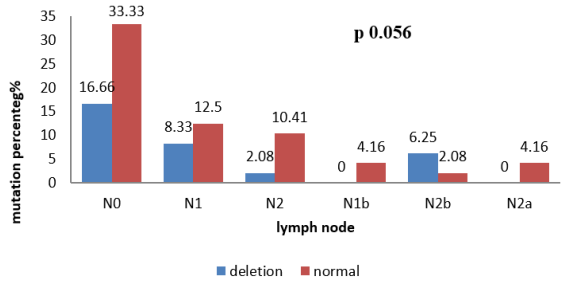

Figure (7) the deletion mutation percentage of (rs10889677) in colon cancer patients according to lymph node

According to several studies, the interaction between the interleukin-23 receptor (IL23R) and IL-23 is necessary for maintaining the T-helper 17 (Th17) response. Th17 mainly causes IL17 production to trigger the release of proinflammatory cytokines. Increasing body of research suggests that IL-23 both speeds up tumor growth and suppresses the immunosurveillance activity provided by CD8 + T cells. Deregulation of IL23R may thereby influence a person's chance of developing cancer (Tang et al., 2014, Ngiow et al., 2013; McKenzie et al., 2006). As was already mentioned, SNPs in the miRNA binding site can change how the miRNA regulates target mRNA expression (Zhang et al., 2014; Bhaumik et al., 2014; Liu et al., 2011).

The rs10889677 variant in the 3 UTR of the IL23R gene was chosen for this study based on analysis of prior research and SNP and miRNA databases (such as miRBase, miRanda, and mirdSNP). This change affects the binding sites for miRNAs Let-7e and Let-7f (Zwiers et al., 2010). Previous studies indicated that this SNP is correlated with IL23R gene expression (Zwiers et al., 2010; Zhou et al., 2013).

Additionally, rs10889677 has been linked to inflammatory bowel disease, a risk factor for colorectal, bladder, and breast cancer, but the data are contradictory (Tang et al., 2014; Wang et al., 2012; Zwiers et al., 2012; Zhou et al., 2013; Omrane et al., 2014; Yao et al., 2014). Here, we looked at the relationship between SNP rs10889677 and sporadic CRC. The incidence of CRC was correlated with environmental and lifestyle risk factors, and the interactions between some of these risk variables and genotypes were assessed. Additionally, the current investigation would detail the pathological findings (167 items). Therefore, further investigation into the function of the rs10880677 A > C polymorphism in the let-7 microRNA binding site of the IL23R in other populations with a larger population size would aid in arriving at a clear understanding of this polymorphism's function and may demonstrate its usefulness as a CRC screening biomarker (Mosallaei et al., 2019).

The deletion mutation in the cancer stage, the highest percentage in III (12.5%), in the I stage was (8.3%) , in the IIb (6.25%) and in the IIA stage was (4.16%) while no deletion mutation appeared in other stages include (II, IV, IIIC and IIC) Figure (8) .

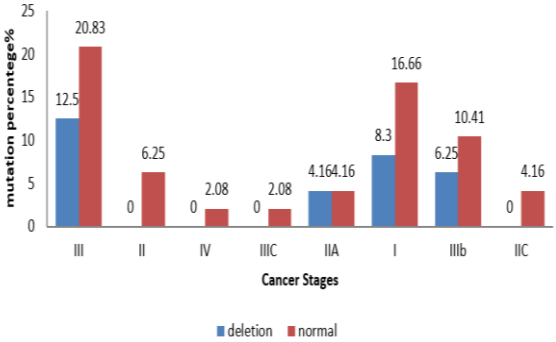

Figure (8) the deletion mutation percentage of (rs10889677) in colon cancer patients according to cancer stage

According to metastasis of cancer the result shows that in the Mx stages the higher normal region with percent (62.5%) and deletion mutation was (4.16%) whlile in the M1 the deletion mutation was (31.25%) and the normal was (2.08%) and no significant obseved amoung metastasis of cancer as shwen in figuer (9)

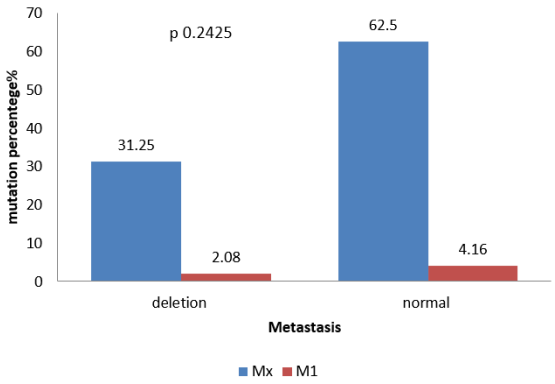

Figure (9) the deletion mutation percentage of (rs10889677) in colon cancer patients according to metastasis

The result of genotyping of SNPs rs10889677 C >A shows the percent of three genotyping homozygotes (CC) and (AA), heterozygote (AC) in both study group, the most common genotyping appeared in patient with colon cancer was heterozygote AC with (18) in patient and (16) in control group and there is no significant differences in both group , the second common genotyping in patient group was homozygotes (CC) with frequency (9) and (2) in control group and there is no significant differences among groups , the last genotyping was homozygotes AA the result shows that this genotyping was more frequent in control group (6) than patient group (5) and there is no significant differences observed as showed in Table (1).

Table (1) distribution of study groups according to g rs10889677 genotyping				
Genotyping Of rs10889677	Patients	Control	Odd ratio (CI95%)	P
AC	18	16	2.0000 0.6853 to 5.8369	0.2046
CC	9	2	3.6000 0.4909 to 26.3992	0.2076
AA	5	6		

The rs10889677 polymorphism might simply make people more susceptible to breast cancer (Liu et al., 2015). In comparison to patients with the wild-type A/A and C/C homozygous genotypes, people with at least one variant C allele of the rs10889677 polymorphism had a higher risk of developing oral cancer and tumor lymph node metastasis. IL23R was also thought to be crucial to the susceptibility and prognosis of ovarian cancer in the Chinese population (Chien et al., 2012). Recent meta-analysis revealed that people with the AC and CC genotype of the rs10889677 polymorphism may have a lower risk of developing multiple solid tumors (P 0.001) (Zheng et al., 2012; Zhou et al., 2013). The C genotype could alter the pace of T-cell proliferation, the percentage of Tregs, and the expression of IL-23R, which further impacted cancer susceptibility. Additionally, IL-23 stimulated the production of IL-17, which is mostly produced by T-cells, accelerating tumor growth by inducing IL-6 and activating STAT3 in malignancies.

The result of rs10889677 genotyping distribution of sub type shows that the heterozygotes AC was more frequent in Adenocarcinoma (9) while homozygotes CC was (7) and AA was (5), in another subgroup Mucinous adeno carcinoma also the heterozygotes AC was more frequent (6) while homozygotes CC was (2) and homozygotes AA was not appeared , and there are no significant differences among sub-type, In the differentiated the mutant heterozygotes AC was most common popular ,in the stages well differentiated was (11) while in the Moderate differentiated (6) and in the high grad (1) and not appeared in Poor differentiated.as shown in Table (2). in the case of Metastases of Lymph node the distribution of mutant heterozygotes AC was higher in N0 with (9)frequent , in N2 was (4) and similar frequent (2) in both N1 and N2a , (1) frequent in N1b and disappeared in N2b, the frequencies of homozygotes CC in spite of lymph node Metastases in each N0,N1 the same frequent (3), in N2,N1b and N2b was (1) and absence in N2a. The result shows the mutant heterozygotes AC was more frequency (16) in Metastases stages Mx while in M1 was less (2) , in the Mx the homozygous CC was (9) and AA (5) while the homozygous CC and AA was disappearance in M1.

Table (2) distribution of patient sub- groups according to rs10889677 genotyping

Subjects	AC	CC	AA	P
Sub-types Mucinus adeno carcinoma Adenocarcinoma	6 9	2 7	0 5	0.0985
Differentiation Well differentiated Moderate differentiated Poor differentiated High grade	11 6 0 1	3 6 0 0	4 1 0 0	0.3477
Lymph node N0 N1 N2 N1b N2b N2a	9 2 4 1 0 2	3 3 1 1 1 0	4 1 0 0 0 0	0.5782
Metastases Mx M1	16 2	9 0	5 0	0.4362

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