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Research Article

Diagnosis of Bladder Cancer by Studying microRNA Gene Variations as a Molecular Genetic Marker

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About Article

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ABSTRACT

Bladder cancer (BC) is one of the most prevalent malignancies worldwide, representing a significant public health burden with high rates of morbidity and mortality. Despite advances in diagnosis and treatment, survival rates for advanced bladder cancer remain suboptimal, highlighting the critical need for a deeper understanding of its pathogenesis and the identification of novel prognostic and therapeutic biomarkers. This study aims to elucidate the association between the miR-146a rs2910164 SNP and bladder cancer risk, as well as its potential impact on gene expression and clinical outcomes in an Iraqi cohort. The study involved a total of 160 participants, comprising 80 patients diagnosed with bladder cancer (case group) and 80 age- and gender-matched healthy individuals (control group). Genotyping was performed using Tetra-ARMS polymerase chain reaction (PCR) followed by restriction fragment length polymorphism (RFLP) analysis. Gel electrophoresis analysis showed that the C allele was more frequent in cases than controls (68 vs. 34), with a significantly association (OR: 1.42, 95% CI: 0.90-2.24; p = 0.029). Conversely, the G allele, while slightly more common in controls (112 v. 106), demonstrated a lower association with cancer susceptibility. Our findings provide robust evidence for the role of the mRNA-seq-associated RNA (miR) 2910164 in bladder cancer, with distinct genotypic patterns and statistical significance between cases and controls.

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1. INTRODUCTION

Bladder cancer (BC) ranks tenth among the most common malignancies globally and sixth among men and involves over 549,000 new cases and 200,000 deaths annually (Saginala *et al.*, 2020). Bladder cancer is a heterogeneous group of pathologies including non-muscle-invasive, muscle-invasive, and metastatic BC with particular molecular and clinical characteristics (Kamat *et al.*, 2016). Over time, diagnosis and therapy have improved, but still have a poor prognosis for invasive BC and necessitate a better understanding of its molecular processes and new diagnostic and predictive biomarkers.

BC development is multifactorial, with environmental exposures such as cigarette smoking and industrial carcinogens, as well as genetic and epigenetic causes, resulting in its development (Lenis *et al.*, 2020; Omar & Ali, 2019). Of the genetic causes, single-nucleotide polymorphisms (SNPs) in carcinogenesis genes have gained increased attention. MicroRNAs (miRNAs)—small non-coding RNAs with functions in gene expression regulation at the post-transcriptional level—are recognized to be core players in cancer biology (Rusca & Monticelli, 2011). Of these, miR-146a has been recognized as a central regulator of inflammation and immune response and has functions in tumor development, such as bladder cancer development (Jazdzewski *et al.*, 2008).

A functional SNP in the miR-146a precursor, rs2910164 (G > C), was shown to regulate miRNA maturation and expressions with effects on downstream targets such as TRAF6 and IRAK1, both part of the NF-κB pathway (Nahid *et al.*, 2009). Polymorphism has had heterogeneous effects in various cancers as a risk or protective factor in a tumor-type-dependent fashion (Ramkaran *et al.*, 2013). Its functional effect and clinical significance in bladder cancer are, however, not established.

Bladder cancer cases have been increasing steadily in Iraq but no genetic study has yet been carried out among the local population. Because of the unique environment and genetics found in Iraq, there is merit examining such polymorphisms as rs2910164 within this context. This study will clarify the connection between the rs2910164 polymorphism of miR-146a and bladder cancer risk among Iraqi individuals. It will also analyze the potential correlation between the SNP, levels of miR-146a expression, and clinicopathological features of the disease.

2. LITERATURE REVIEW

Bladder cancer is still a global health issue, and a large literature has examined its molecular and genetic etiology. Much evidence has solidified evidence for environmental exposure—primarily tobacco smoke and chemicals from industry—being central to causation (Lenis *et al.*, 2020; Kamat *et al.*, 2016). At the same time, there has been increasing focus on clarification of genetic polymorphisms influencing control of interindividual susceptibility, with particular interest directed towards those found within non-coding loci such as microRNAs (Li *et al.*, 2010; Rusca & Monticelli, 2011).

Among the miRNAs implicated in carcinogenesis, miR-146a stands out for its dual role in modulating inflammation and regulating gene expression pathways involved in cancer development. The rs2910164 G>C polymorphism within the precursor region of miR-146a has been linked to altered miRNA processing and decreased mature miR-146a levels. This, in turn, affects the regulation of key targets like TRAF6 and IRAK1, which are central to NF-κB signaling, a pathway strongly implicated in tumorigenesis (Nahid *et al.*, 2009; Jazdzewski *et al.*, 2008). Several studies have evaluated this polymorphism in various cancer types—including thyroid, breast, and prostate cancers—with conflicting results regarding its oncogenic or protective roles (Xu *et al.*, 2014; Ramkaran *et al.*, 2013).

However, despite the abundance of global data, there remains a critical lack of studies examining this polymorphism in bladder cancer within Middle Eastern populations, and more specifically, among Iraqis. Given the country's distinctive environmental risk profile—including widespread smoking, occupational exposure to carcinogens, and genetic diversity—extrapolating findings from Western or East Asian populations may not be appropriate or sufficient (Omar & Ali, 2019; Saginala *et al.*, 2020). Genetic variations often show population-specific frequency and functional impact, further reinforcing the need for region-specific research.

To date, few, if any, studies have assessed the role of miR-146a rs2910164 in bladder cancer susceptibility among Iraqi patients. This represents a significant gap in the literature, particularly given the increasing incidence of BC in the region. Addressing this void could contribute to a more nuanced understanding of bladder cancer pathogenesis and support the development of targeted diagnostics or preventive strategies tailored to Iraq's unique genetic and environmental landscape.

3. METHODOLOGY

3.1. Study design and population

The hospital-based case-control study was used to investigate the association of the miR-146a rs2910164 polymorphism with bladder cancer risk in the Iraqi population. We enrolled 160 subjects in this study, with 80 confirmed bladder cancer patients and 80 age- and sex-matched healthy controls. The patients were newly diagnosed with bladder cancer, as identified through histopathological diagnosis. Patients were recruited from the oncology departments of three of Najaf's largest hospitals, including Al-Sadr Medical City, Al-Furat Al-Awsat Hospital, and Al-Hakim General Hospital. Of note, the patients were treatment-naive at the time of study entry—there was no history of chemotherapy, radiotherapy, or of targeted treatment for their cancer. Medical histories and pathology reports were carefully screened to verify each diagnosis and to document clinical data.

The control subjects were obtained from the general outpatient populations of the respective hospitals. These were patients with neither family nor personal histories of bladder or other cancers and who were coming in for routine follow-up visits or for the treatment of minor, non-cancerous complaints. In an attempt to control for confounding variables as well as to eliminate bias, the control subjects were systematically matched with the cases for age, sex, occupational exposure to known bladder carcinogens (e.g., chemical dyes, industrial solvents), and smoking. This stringent design was used to make the groups more uniform and increase the reliability of the detected genetic associations.

3.2. DNA Extraction and genotyping

3.2.1. Sample collection and processing

All the patients provided peripheral blood samples of almost 3 mL in sterile ethylenediaminetetraacetic acid (EDTA) tubes in view of preventing the coagulation of the blood and maintaining the integrity of the nucleic acid. The samples were labeled suitably to make them identifiable and trackable. The blood samples were stored at 4°C immediately in an attempt to maintain the samples, and were handled to extract DNA within a fixed time to maintain the integrity of the genomic material for subsequent purposes.

3.3. DNA Extraction

Genomic DNA was extracted from the collected blood samples using the Intron G-spinTM Total DNA Extraction Kit Korea according to the manufacturer's protocol. The extraction process involved the following critical steps:

3.4. DNA Extraction

Genomic DNA was extracted from the collected blood samples using the CinnaGen DNA Purification Kit (CinnaGen, Iran) according to the manufacturer's protocol. The extraction process involved the following critical steps:

i. Cell Lysis: Red blood cells and other cellular components were lysed to release nuclear material.

ii. Protein Precipitation: Proteins and impurities were removed to ensure the purity of the genomic DNA.

iii. DNA Precipitation and Isolation: DNA was precipitated using alcohol and subsequently purified.

iv. Washing and Resuspension: The DNA was washed to remove residual contaminants and resuspended in an appropriate buffer for downstream analyses.

The concentration and purity of the extracted DNA were assessed using a NanoDrop spectrophotometer, measuring the absorbance ratios at 260/280 nm and 260/230 nm to ensure high-quality DNA suitable for genotyping.

3.5. Genotyping analysis by Tetra-ARMS PCR

The miR-146a rs2910164 polymorphism was genotyped using Tetra-ARMS PCR with restriction fragment length polymorphism (RFLP) analysis. Amplification of the target segment with the SNP was carried out using specific primers (Table 1).

Table 1. Primer sequences and expected product sizes

Primer	Sequence 5′ - 3′	PCR product
Primer-F (Allele-C)	5′- tccatgggttgtgtcagtgtcagagctc-3′	290bp
Common Primer-R	5′- gagtagcagcagcagcaagagagactt-3′	
Common Primer-F	5′- tagacctggtactaggaagcagctgcat-3′	203bp
Primer-R (Allele-G)	5′- atatcccagctgaagaactgaattacac-3′	
Common Primer-F	5′- tagacctggtactaggaagcagctgcat-3′	445 bp
Common Primer-R	5′- gagtagcagcagcagcaagagagactt-3′	

3.6. PCR Conditions

The PCR reaction was performed in a total volume of 12.5 µL containing (Table 2). The thermal cycling conditions were optimized to ensure the specific amplification of the target polymorphism are detailed in Table 3.

Table 2. PCR Reaction mixture promega

Reagent	Volume (µL)
Master Mix 2X	12.5
Forward common Primer	1
Reverse common Primer	1
G allele	1
C allele	1
DNA template	3.5
Nuclease-free water	5

The amplified products were digested with a specific restriction enzyme targeting the SNP site and analyzed by gel electrophoresis. The resulting fragments were visualized under UV light to determine the genotype of each sample.

Table 3. Thermal cycling parameters

Step	Temperature (°C)	Time	Number of Cycles
Pre-denaturation	95	5 min	1
Denaturation	95	30 sec	35
Annealing	59	30 sec	35
Extension	72	90 sec	35
Final Extension	72	10 min	1
Storage	4	∞	

The 2% ethidium bromide-stained agarose gel was used to resolve the amplicons to detect the PCR product. Based on the pattern of the band, allelic variants of the rs2910164 polymorphism were accurately detected. The electrophoresis was performed in the laboratory to give accurate and reproducible results. Genotypic patterns were detected depending on the size of the DNA band in the gel:

i. GG (Wild Type): Bands at 203 bp and 445 bp.
ii. GC (Heterozygote): Bands at 203 bp, 290 bp, and 445 bp.
iii. CC (Mutant Type): Bands at 290 bp and 445 bp.

These banding patterns provided reliable data for subsequent statistical analyses, ensuring the robustness of the genotyping procedure.

3.7. Statistical analysis

Genotypic and allelic frequencies for the controls and the bladder cancers were also analyzed to ascertain the strength of association using Fisher's exact test. Odds ratios (OR) with 95% confidence intervals (CIs) were used in estimating the strength of the risk of the genotypes as well as the alleles. The contribution of rs2910164 polymorphism of miR-146a to the susceptibility to bladder cancer was considered significant if $p < 0.05$.

4. RESULTS AND DISCUSSION

The result showed the genotyping of the miR-146a rs2910164 (G>C) polymorphism by the Tetra-ARMS PCR and 2% ethidium bromide-stained agarose gel with a clear and distinct pattern of bands of the three possible genotypes. The GC heterozygous genotype was represented with the 203 bp, 290 bp, and 445 bp bands for the occurrence of the G and the C alleles together. The homozygous CC genotype (mutant type) was represented by the 290 bp and 445 bp bands with the absence of the wild-type allele G. The GG homozygous genotype (wild type) was represented with the 203 bp and 445 bp bands with the absence of the mutant allele C. In the gel, a 100 bp molecular weight marker was added to the first well to serve as a size marker in the identification of the amplified fragments. The occurrence of the 445 bp inner control band in the samples validated successful amplification, which is indicative of the integrity of the PCR reaction.

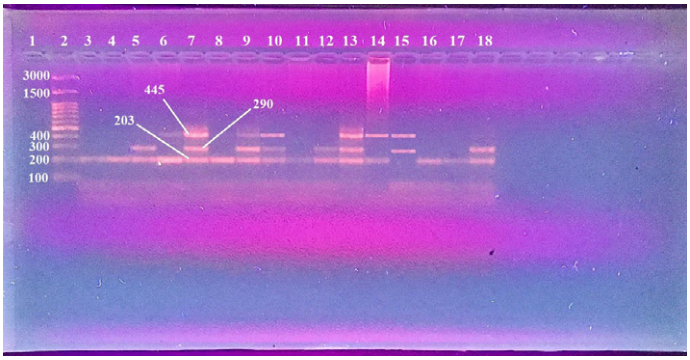

Figure 1. Tetra-ARMS PCR Results for rs2910164 (G>C) Polymorphism in the miR-146a Gene on a 2% Agarose Gel

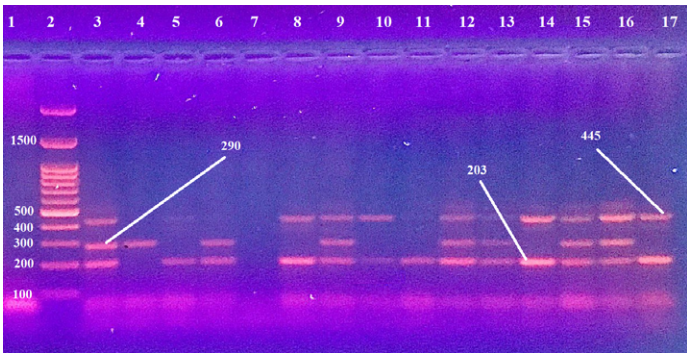

Figure 2. Control Tetra-ARMS PCR Results for rs2910164 (G>C) Polymorphism in the miR-146a Gene on a 2% Agarose Gel

The electrophoresis of the Tetra-ARMS PCR products results in a well-readable and discernible banding pattern of the miR-146a rs2910164 (G>C) polymorphism. All of the genotypes were correctly identified based on the size and number of the specific bands: the GC heterozygote presented bands at 203 bp, 290 bp, and 445 bp, indicating the existence of both alleles; the CC homozygote (mutant allele) presented bands at 290 bp and 445 bp, indicating the absence of the G allele; and the GG homozygote (wild-type allele) presented bands at 203 bp and 445 bp, indicating the absence of the C allele. Also loaded on the gel was a 100 bp molecular weight marker as size marker so that there would be an accurate determination of the amplified fragments. The uniform appearance of the 445 bp control band in all the samples ensured the success and integrity of the amplifications. These results validate the strength, specificity, and reproducibility of the Tetra-ARMS PCR assay for the genotyping of the rs2910164 polymorphism. The assay is well suited to use in association studies, especially in evaluating the association of miR-146a polymorphisms and the risk of cancers including bladder cancer, as in the current research.

Electrophoresis of the Tetra-ARMS PCR products of the rs2910164 (G>C) polymorphism of the miR-146a on 2% ethidium bromide-stained agarose also provided distinct, readable banding of the genotypes. The 203 bp and 445 bp bands of the GG homozygote (wild-type) ensured the absence of the mutant allele C. The 290 bp and 445 bp bands of the CC (mutant type) homozygote established the absence of allele G. The 203 bp, 290 bp, and 445 bp bands of the GC (heterozygote) established the presence of both alleles. It also incorporated 100 bp molecular weight marker for proper sizing of the PCR product during the process of correct genotypic determination. The well-spaced pattern of the 445 bp control band in each of the samples was a sign of successful amplification corresponding to the technological process quality. All the observations confirm the reproducibility and reliability of the Tetra-ARMS PCR process to identify the polymorphism of rs2910164. The reproducibility and clean banding pattern observed confirm this protocol as one of the validated processes for the allelic variation determination and its probable usage in the genetics of association studies, in particular, the determination of the role of miR-146a in the susceptibility to disease in diseases like cancer.

The electrophoresis of the rs2910164 polymorphism in the miR-146a gene Tetra-ARMS PCR products generates reproducible and clear banding patterns for all the genotypes. The GG (wild type) is detected by 203 bp and 445 bp bands, the CC (mutant type) by 290 bp and 445 bp bands, and the GC (heterozygote) by 203 bp, 290 bp, and 445 bp bands.

Lane 1 is the 100 bp molecular weight marker, which is utilized as a size marker to accurately measure the size of the fragments. The appearance of the 445 bp control band in all of the samples consistently verifies successful amplification. The photograph shows the accuracy of the Tetra-ARMS PCR assay in genotyping

the rs2910164 polymorphism, confirming the reliability of the assay as a probe for the use in genetic association studies.

4.1. Genotypic and allelic frequencies

The results describe the different genotypes and the gel electrophoresis assay of the rs2910164 variant of the miR-146a gene, which is found to demonstrate apparent differences in the banding pattern and the main statistics of the bladder cancer cases and the normal controls. Genotypically, the most common was the GC genotype in the bladder cases with 48 of 90 of the cases having this and was represented as the 203 bp, 290 bp, and 445 bp triple bands. This combination of the genotype was significantly more at risk of bladder cancer with an odds ratio (OR) of 2.72 (95% CI: 1.46–5.10; p = 0.001). The GG genotype, represented as the 203 bp and 445 bp double bands, was more common in the controls (42 of 70) and was linked with the lower risk of bladder cancer (OR: 0.59, 95% CI: 0.33–1.03; p = 0.021). The CC genotype, represented as the 290 bp and 445 bp double bands, was comparatively infrequent and was detected in 10 cases and 6 controls, with an OR of 1.94 (95% CI: 0.62–6.01; p = 0.035). Allelic frequency analysis showed that the C allele was more frequent in cases than controls (68 vs. 34), with a significant association (OR: 1.42, 95% CI: 0.90–2.24; p = 0.029). Conversely, the G allele, while slightly more common in controls (112 vs. 106), demonstrated a lower association with cancer susceptibility (OR: 0.83, 95% CI: 0.59–1.18; p = 0.043). These findings, validated by the gel electrophoresis analysis, underscore the relevance of the rs2910164 polymorphism in miR-146a as a genetic determinant in bladder cancer, with distinct genotypic patterns and statistical significance between cases and controls. While the genotypic and allelic distribution showed statistically significant associations—particularly the GC genotype (OR: 2.72, p = 0.001) and C allele (p = 0.029)—it is important to interpret these values with caution due to the relatively small sample size (n=160). The study did not apply a correction for multiple hypothesis testing (e.g., Bonferroni or Benjamini-Hochberg adjustments), which may increase the risk of type I errors. Therefore, although the findings suggest a potential association, further validation in larger, independent cohorts is required. The genotypic distribution and statistical analysis are summarized in Table 3.

Table 3. Genotypic and allelic frequencies with statistical analysis

Genetic marker/Allele	Patients (n=90)	Controls (n=70)	Odds Ratio (95% CI)	p-value
G Genetic marker	112	106	0.83 (0.59–1.18)	0.043
C Genetic marker	68	34	1.42 (0.90–2.24)	0.029
GG	32	42	0.59 (0.33–1.03)	0.021
CC	10	6	1.94 (0.62–6.01)	0.035
GC	48	22	2.72 (1.46–5.10)	0.001

4.2. Discussion

The outcomes of this research strongly support the association of the miR-146a rs2910164 polymorphism with susceptibility to bladder cancer in the Iraqi population. Specifically, the risk of bladder cancer was significantly increased in patients with the GC genotype (OR = 2.72, p = 0.001), with a protective effect observed for the GG genotype (OR = 0.59, p = 0.021). These outcomes were in line with the research findings indicating the biological significance of miR-146a in tumorigenesis, in particular its role in the modulation of inflammatory and immune-related signal transduction, playing critical roles in tumorigenesis (Li *et al.*, 2010; Jazdzewski *et al.*, 2008). The results herein validate the supposition that the genetic variants of the miR-146a would affect the risk of patients with cancer by disrupting its regulatory function, and rs2910164 can serve as a susceptibility marker to risk-stratify bladder cancer in this population in the region.

MicroRNA-146a is a critical modulator of the NF-κB pathway by targeting its critical adaptor proteins IRAK1 and TRAF6, which are central to tumor formation and to the development of inflammation (Nahid *et al.*, 2009). The rs2910164 polymorphism with G > C substitution in the precursor of miR-146a has also been reported to alter the processing of miR-146a and to reduce the level of mature miR-146a. Such a disruption in the function of miRNA reduces the ability of miRNA to silence oncogenic targets. Jazdzewski *et al.* (2008) demonstrated that the C allele results in reduced levels of mature miR-146a with the resulting loss of its tumor suppressive function and the likely outcome of increased susceptibility to cancer. This mechanism is supported by our results: the C allele was significantly more frequent among patients with bladder cancer in comparison with controls (p = 0.029), as would be expected of a susceptibility allele. These findings confirm the biological relevance of miR-146a deregulation in tumor formation and point to the rs2910164 as a putative biomarker of bladder cancer susceptibility.

Correspondingly, many studies have examined the contribution of the rs2910164 polymorphism to oncologic heterogeneity across a spectrum of cancers with generally confirmatory but also inconsistent findings. For instance, research in thyroid carcinoma (Jazdzewski *et al.*, 2008) and breast cancer (Xu *et al.*, 2014) has identified the GC and CC genotypes to correlate with increased risk of the respective cancers, continuing to support the idea that this polymorphism interferes with the tumor suppressor function of miR-146a. But contrasting observations have also been reported in the context of prostate cancer in which Shi-Lung Lin *et al.* (2008) reported a protective function of the same polymorphism. Such inconsistencies could arise from tissue-specific functions of miR-146a, as its targets of regulation and biological impacts may significantly differ in different cellular conditions and tumor types. Such inconsistencies indicate the complexity of the function of miR-146a and the need for investigations specific to the type

of cancer. For bladder cancer, further functional and clinical studies are necessary to describe the exact function of rs2910164 and to determine if this can be utilized as a useful biomarker or therapeutic target.

Contrary to certain studies on bladder cancer, this study's findings are in close agreement with the existing line of evidence emphasizing the genetics of inflammation. Kamat *et al.* (2016) noted the involvement of genetic polymorphism in the inflammation processes to reveal that these sorts of alterations—especially in microRNA—are likely to affect tumor development and promote immune evasion mechanisms. Sanli *et al.* (2017) also noted the regulatory function of miR-146a in modulating the interactions between the tumor and microenvironment as a central mechanism of bladder caner pathogenesis. Our data confirm these conclusions with a significant association between the rs2910164 polymorphism and bladder cancer risk. Both the increased frequency of the GC genotype and allele C in bladder cancers in this study emphasize the functional significance of miR-146a dysfunction. These findings are in line with the expectation that polymorphisms of miR-146a not only can modulate the susceptibility to cancer in patients but also the biologic behavior of tumors via their control of the processes of anti-inflammation and regulation of the immune system. Collectively, this line of evidence is compatible with the new consensus that miRNA variants such as rs2910164 play an important role in the molecular pathogenesis of bladder cancer (Omer *et al.*, 2019).

Also, note that in the allelic analysis, we detected the rs2910164 C allele to have a significant association with bladder cancer risk over the wild-type allele ($p = 0.029$). This is in agreement with Ramkaran *et al.* (2013), where the latter reported that the C allele is linked to lower levels of the mature miR-146a. Downregulation of the miR-146a reduces its activity to modulate the mediators of inflammation such that there is overexpression of the pro-inflammatory genes IRAK1 and TRAF6.

These genes are regulatory players of the NF-κB pathway and are involved in tumor-propagating inflammation, which is recognized to be a hallmark of cancer. These genes contribute to the creation of a tumorigenic microenvironment if overexpressed, in which processes such as evasion of the immune response, angiogenesis, and tissue remodeling are facilitated. These findings thus contribute to the functional significance of the rs2910164 polymorphism in the process of cancer-associated inflammation as well as point toward its potential as a genetic susceptibility marker of bladder cancer.

Notably, the current research is the first to investigate the rs2910164 polymorphism in an Iraqi population and offer new data concerning the genetics of bladder cancer risk in this hitherto poorly studied population. As prior research has focused mainly on Europeans and Asians, the current research contributes to a more universal appreciation of how local environment and genetics interact to contribute to the risk of cancer. Iraq's unique environmental exposures as well as its genetic diversity—primarily the pervasive smoking and workplace exposures to established bladder carcinogens—underscore the merit of research in this setting to understand gene-environment interactions (Lenis *et al.*, 2020; Omar *et al.*, 2024).

Despite its contribution, the study is not without limitations. Its modest sample size might inhibit the power of the statistics and the generalizability of the findings. Larger, multicenter cohort studies are needed in the future to corroborate and reinforce these associations. Moreover, while the findings point to an important functional role of the rs2910164 polymorphism in bladder carcinogenesis, in vitro and in vivo functional studies would be needed to establish its direct impact on the mechanism of miR-146a biogenesis, on the regulation of its target genes, and its overall function in bladder tumorigenesis. Pursuing this line of investigation further would also have the potential to form the basis of the inclusion of miR-146a genotyping in risk modeling and personalized treatment strategies in the Iraqi population and in other populations.

5. CONCLUSION

In conclusion, our findings provide robust evidence for the role of the rs2910164 polymorphism in miR-146a as a genetic determinant of bladder cancer susceptibility in the Iraqi population. The significant association of the GC genotype and C allele with increased risk underscores the importance of miR-146a in bladder cancer pathogenesis. These results contribute to the growing body of evidence supporting the utility of miRNA polymorphisms as potential biomarkers for cancer risk assessment and therapeutic targeting.

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