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The Role of rs10811661 Polymorphism in the CDKN2A/B Gene: A Narrative Review of Prognostic Biomarker for Colon and Gastric Cancers

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Abstract

Context: The rs10811661 polymorphism in the CDKN2A/B gene has emerged as a potential prognostic biomarker for colon and gastric cancers, both of which significantly contribute to global cancer mortality. Identifying genetic factors that influence cancer progression is crucial for enhancing early detection and patient outcomes. This narrative review explores the molecular mechanisms by which rs10811661 impacts tumor development, particularly its role in cell cycle regulation, insulin signaling, and ANRIL, a long non-coding RNA involved in gene expression modulation.

Evidence Acquisition: The present research indicates that patients with the TT genotype of rs10811661 are at a higher risk of developing more aggressive and invasive forms of colon and gastric cancer. In colon cancer, the TT genotype is linked to advanced tumor stages and increased invasiveness, with notable sex-specific differences, particularly among female patients.

Results: In gastric cancer, this polymorphism is associated with earlier onset and rapid progression, especially in younger patients carrying the TT genotype. The rs10811661 polymorphism shows promise as a diagnostic and prognostic marker, allowing clinicians to stratify patients based on genetic risk and personalize treatment approaches.

Conclusions: Integrating genetic testing for rs10811661 into routine clinical assessments could enhance early detection and optimize cancer management strategies. Further research is needed to explore its broader implications across other cancers and its interactions with environmental factors, including lifestyle and diet.

Keywords: rs10811661 Polymorphism, CDKN2A/B Gene, Colon Cancer, Gastric Cancer, Biomarker, Tumor Invasiveness

1. Context

Gastric cancer and colon cancer are two of the most prevalent cancers with extensive effects on cancer mortality rates. Gastric cancer ranks as the fifth most common cancer in the world, resulting in over 800,000 deaths annually, whereas colorectal cancer is the third most common and the fourth most common cause of cancer death. In spite of improvements in diagnostic and therapeutic strategies, both types of cancer are usually diagnosed at more advanced stages due to nonspecific early symptoms, which result in unfavorable outcomes (1, 2). The etiological factors involved in these cancers are complex, including lifestyle, diet, advancing age, and genetic predisposition. Among these factors, genetic polymorphisms have been given heightened attention for their involvement in cancer susceptibility and development. Alterations of key regulatory genes, like CDKN2A/B, affect the risk of cancer by modulating the expression of oncogenes and tumor suppressor genes (3, 4).

The CDKN2A/B gene encodes significant tumor suppressor proteins that are involved in the regulation of the cell cycle, particularly in suppressing abnormal cell growth. Polymorphisms in this gene have been linked to a variety of cancers, including breast, pancreatic, and colorectal cancers. A polymorphism,

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rs10811661, in the CDKN2A/B gene locus has been found to be a potential biomarker for the early diagnosis and prognosis of colon and gastric cancers. Yet, research on rs10811661 reveals contradictory results about its clinical relevance; some research links it with enhanced tumor invasiveness and poor prognosis, whereas others indicate that its effect may be conditional upon various factors like age, sex, and environmental influences.

This narrative review seeks to consolidate the current evidence of research on rs10811661, its implication in cancer development, and its potential clinical relevance in cancer outcome prediction. Through the evaluation of recent literature, especially those examining genetic samples of colon and gastric cancer patients, we seek to clarify the influence of rs10811661 on tumor biology. In addition, we will discuss its prospects as a diagnostic and prognostic biomarker while highlighting important areas of future research.

2. Molecular Mechanisms Associated with the CDKN2A/B Gene

CDKN2A/B is a tumor suppressor and cell cycle regulator gene. The gene produces proteins that are inhibitors of cyclin-dependent kinases CDK4 and CDK6, which are key players in the G1 to S phase transition in the cell cycle. The inhibition of these kinases prevents uncontrolled cellular growth, which is a hallmark of cancer development. The two important tumor suppressor proteins that are encoded by this gene, $p16^{INK4A}$ and $p14^{ARF}$, play significant roles in tumor suppression mechanisms (5-8).

Polymorphism rs10811661 in the non-coding region of CDKN2A/B was found to be a single nucleotide polymorphism (SNP) that may have significant effects on cancer susceptibility. While it does not change proteins directly, rs10811661 affects the expression levels of adjacent genes, including tumor suppressor genes. This particular polymorphism has been associated with decreased expression of $p16^{INK4A}$, which interferes with the regulation of the G1 phase, ultimately causing uncontrolled cell division and tumor development (9, 10).

One of the key pathways influenced by CDKN2A/B is the insulin signaling pathway, which has been implicated in many cancers, including colorectal cancer. Insulin receptors play a critical role in cellular growth, metabolism, and apoptosis, and their deregulation is associated with the process of tumorigenesis. Genetic polymorphisms linked with insulin resistance, including those in CDKN2A/B genes, have been found to enhance cancer susceptibility through the modulation of insulin receptor activity. The rs10811661 polymorphism has been hypothesized to disrupt insulin signaling, thus lowering the expression of genes involved in glucose metabolism and cell survival regulation, consequently facilitating cancer development (11-13).

Furthermore, the function of ANRIL, an lncRNA within the CDKN2A/B locus, has been a subject of extensive investigation in cancer biology. ANRIL modulates CDKN2A/B expression via epigenetic pathways, including histone modification. Overexpression of ANRIL has been associated with tumor development and adverse prognosis in colorectal cancer. Through altering chromatin structure, ANRIL suppresses CDKN2A/B expression, reducing the tumor-suppressing function of $p14^{ARF}$ and $p16^{INK4A}$, resulting in unchecked cell cycle progression (14).

Furthermore, aberrant methylation of the CDKN2A/B locus plays an important role in its tumor suppressor activity. Epigenetic alterations, particularly hypermethylation, lead to gene silencing, which is frequently observed in gastric and colorectal cancers. The methylation status of this gene is progressively being recognized as a potential biomarker for cancer development and prognosis, as it correlates with poor clinical outcomes (15, 16).

3. Association of rs10811661 Polymorphism with Colon Cancer

Colon cancer is among the most common types of cancer globally, and hereditary factors contribute significantly to its etiology. Surprisingly, the rs10811661 polymorphism of the CDKN2A/B gene has been recognized as a potential biomarker whose effect could modify susceptibility to and progression of the disease. The subsequent section examines the evidence implicating rs10811661 in colon cancer and its effect on tumor invasiveness, histological grading, and overall prognosis (17, 18).

4. Key Findings in Colon Cancer

Various studies have reported a strong correlation between the rs10811661 polymorphism and colorectal cancer, particularly with regard to the aggressiveness of the tumor and disease progression. In one cohort study involving 400 subjects, where 100 were patients diagnosed with colorectal cancer, rs10811661 was genotyped using PCR techniques. The findings revealed that patients with the TT genotype exhibited a

significantly increased risk of developing invasive tumors and advanced stages of the disease compared to their counterparts who had the CC genotype. It is notable that 46% of the subjects with the TT genotype had tumors that were invasive at the T3 stage, suggesting a potential role of this polymorphism in tumor progression (19).

Later statistical analyses have confirmed the role of rs10811661 in tumor aggressiveness. Studies show that the TT genotype is more common in patients with stage II and III tumors compared to the CC genotype, which is largely present in those who present with early-stage tumors (stage I). These findings suggest that rs10811661 may play a role in tumor invasiveness and metastatic potential, thereby being a significant factor in colon cancer progression (19-21).

5. Sex-Specific Differences

The involvement of sex in the rs10811661 polymorphism and its consequence on the progression of colon cancer is a remarkable area of research. In the same cohort study, there were conspicuous differences in the distribution of genotypes and tumor characteristics by sex. Women had a greater proportion of advanced-stage tumors as well as a greater frequency of the TT genotype than men. Female patients, in general, had a higher propensity to have T3-stage tumors, as indicated by their greater invasiveness (22).

It was found that male patients were more likely to be diagnosed with stage I tumors and had a higher propensity to have the CT genotype. The result indicates the protective role of the CT genotype in males against tumor progression. The differences observed across sexes may be under the control of hormonal or metabolic processes that can differentially regulate the role of rs10811661 in colon cancer pathogenesis (22, 23).

6. Clinical Significance

The identification of the rs10811661 polymorphism as a potential biomarker for colon cancer has immense significance in clinical practice. Firstly, the polymorphism can be utilized as a diagnostic indicator to identify individuals at higher risk of developing invasive or advanced-stage colon cancer. For instance, individuals with the TT genotype may benefit from intensified screening protocols comprising earlier initiation and more frequent colonoscopic screening with the objective of identifying tumors at an early stage. The rs10811661 polymorphism can also be utilized as a prognostic biomarker to foresee disease trajectories and inform treatment decisions. Individuals with the TT genotype, found to be at high risk for developing invasive and advanced neoplasms, may need more intensive treatment modalities, including chemotherapy, even at an early stage of the disease. Furthermore, the fact that this polymorphism is linked to tumor invasiveness and grade makes it a valuable marker for the stratification of patients into varying risk categories, enabling more personalized treatment strategies (20-25).

7. Association of rs10811661 Polymorphism with Gastric Cancer

Gastric cancer remains a serious worldwide health concern, ranking as the third most common cause of cancer death worldwide. Environmental and hereditary factors are implicated in its development, and the rs10811661 polymorphism of the CDKN2A/B gene has been reported as a potential genetic risk and progression factor of the disease. In this section, the involvement of rs10811661 in gastric cancer is presented, focusing on its association with tumor stage, invasiveness, and prognosis (26-28).

8. Key Findings in Gastric Cancer

Research on rs10811661 has revealed strong associations between this polymorphism and gastric cancer progression, including invasiveness and the stage of cancer at diagnosis. In 100 gastric cancer patients, a study found the TT genotype to be most common among subjects with advanced-stage tumors; among these subjects with the TT carrier genotype, 46% had T3-stage cancers, where tumor invasion is deep into gastric and adjacent tissues. Conversely, the CC genotype was found at a higher frequency in tumors of early-stage (stage I) classification, suggesting a role for rs10811661 in the regulation of tumor progression (29, 30).

These findings imply that the rs10811661 polymorphism has a two-fold role in not only predisposing individuals to gastric cancer but also influencing the severity of the disease. In particular, the TT genotype is indicative of poorer prognosis, as it is correlated with higher tumor invasiveness (30, 31).

9. Age and Tumor Progression

Age is a determining factor in the development of gastric cancer, and most cases are diagnosed in patients above 60 years old. However, it has been noted that rs10811661 also plays a role in younger patients. In a study of a series of gastric cancer patients between the

ages of 25 - 52, the TT genotype was significantly more common in patients between 35 - 43 with late-stage (stage II and III) tumors. These findings imply that individuals with the TT genotype can develop aggressive gastric cancer at an earlier age relative to those with the CC or CT genotypes. Conversely, older patients were most likely to have the CC genotype, and this was found to be associated with early-onset tumors. These findings uphold a possible age-dependent role of rs10811661 and may guide age-specific screening and treatment approaches in populations at risk (32, 33).

10. Potential for Early Diagnosis and Prognosis

The rs10811661 polymorphism is a highly promising biomarker for the early diagnosis and prognostic evaluation of gastric cancer. Individuals with the TT genotype, especially those who are diagnosed at a young age, can potentially benefit from closer surveillance and early treatment. Since gastric cancer is often diagnosed at a late stage because of nonspecific symptoms, the detection of individuals at high genetic risk may enable earlier diagnosis and better survival. Prognostically, the rs10811661 polymorphism may enable patient stratification according to genetic risk of developing more aggressive types of the disease. For example, patients with the TT genotype may be potential candidates for receiving more aggressive treatment modalities upfront despite the absence of advanced-stage tumors. This strategy may avert the advancement of the disease and enhance overall patient outcomes (34, 35).

11. Implications for Future Research and Clinical Practice

The results of the rs10811661 polymorphism of the CDKN2A/B gene have opened up new possibilities for research and clinical application in the control of colon and gastric cancers. In this section, the discussion will focus on the wider implications of the findings, specifically how they are likely to inform future research directions as well as clinical decisions regarding the diagnosis, prognosis, and treatment of these cancers (27, 36).

12. Prognostic Value of rs10811661

The polymorphism rs10811661 has been very promising as a prognostic indicator for both colon and gastric cancers. In various studies, including the one being reviewed in this article, the TT genotype has been consistently linked to more aggressive tumor characteristics and cancers at later stages. This would mean that the rs10811661 polymorphism can be used to identify those patients who are at higher risk of poor outcomes, allowing clinicians to stratify individuals based on genetic background. Clinically, the addition of genetic information such as the rs10811661 polymorphism to the usual cancer assessments could revolutionize personalized medicine. For example, individuals with the TT genotype can receive closer monitoring and aggressive treatment from the initial stages of their disease, thereby enhancing their survival rates. Additionally, the incorporation of genetic testing for rs10811661 in standard evaluations for individuals who are determined to be at high risk of colon or gastric cancer, especially in patients with a family history of cancer, would be helpful (34-39).

13. Integration with Genetic Testing

One of the main clinical uses of the rs10811661 polymorphism is its potential for application in genetic testing. As genetic testing becomes increasingly available, the application of high-risk polymorphisms such as rs10811661 may result in early detection, risk determination, and treatment planning. Individuals with the TT genotype may be able to gain advantage through the implementation of earlier and more frequent screening interventions, i.e., colonoscopies for detecting colorectal cancer and endoscopies for identifying gastric malignancy, enabling the detection of tumors at a phase that is more receptive to treatment (40, 41).

Rs10811661 genetic testing can also prove helpful in determining personalized treatment strategies. Patients who have this genetic polymorphism, especially those with aggressive forms of tumor, may need customized treatment strategies, like targeted therapy or a blend of therapies, to adequately manage the more invasive features of their cancer. By using treatment regimens tailored to a patient's genetic composition, medical providers may be able to significantly enhance patient outcomes and lower the risk of cancer recurrence (42).

14. Areas for Further Study

In spite of the encouraging results involving the rs10811661 polymorphism, various points require additional exploration. First, although the association of this polymorphism with colon and gastric cancers is clear, additional research is warranted to determine its role in other malignancies and to explore its interaction with lifestyle and environmental factors. Analyzing the

prospective impacts of diet, smoking, alcohol consumption, and physical exercise on the rs10811661 polymorphism effect can provide important insight into the prevention strategies of cancer in people with genetic predispositions.

Moreover, one area for future research is the elucidation of the sex-specific differences observed in colon cancer patients. The research covered in this review brought to the forefront that women patients who had the TT genotype were more prone to having late-stage tumors when compared to their male equivalents. Gaining insight into the biological processes underlying these sex disparities may result in more specific treatment for female cancer patients and the implementation of sex-specific therapeutic regimens (43-48).

Additionally, the function of the ANRIL long non-coding RNA in the regulation of the CDKN2A/B locus, along with its association with the rs10811661 polymorphism, is an exciting avenue of study. Further research into ANRIL's epigenetic control of tumor suppressors and its potential as a drug target may reveal new treatment options for individuals with this genetic configuration.

15. Conclusions

The rs10811661 polymorphism in the CDKN2A/B gene has emerged as a crucial genetic factor in the development and progression of both colon and gastric cancers. This polymorphism is significantly associated with tumor invasiveness, advanced stages, and poor prognosis, particularly in patients with the TT genotype. The findings reviewed in this article highlight the polymorphism's potential as a diagnostic and prognostic biomarker, enabling earlier detection and more personalized treatment strategies for high-risk individuals.

The role of rs10811661 in modulating key molecular pathways, including cell cycle regulation and insulin signaling, underscores its importance in cancer biology. Moreover, its association with the ANRIL non-coding RNA and epigenetic regulation further complicates its influence on tumor suppression, offering potential targets for future therapeutic interventions.

Moving forward, the integration of genetic testing for the rs10811661 polymorphism into clinical practice could enhance early diagnosis and provide critical insights for tailoring personalized treatment plans. Further research is required to explore the broader implications of this polymorphism across other cancer types, as well as its interaction with environmental and lifestyle factors. By expanding our understanding of rs10811661 and its role in cancer development, the medical community can continue to make strides toward improved outcomes for patients with colon and gastric cancers.

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