American Journal of Social and Humanitarian Research

Vol. 5 Issue 6 | pp. 12-21 | **e-ISSN:** 2690-9626
Available online @ https://www.globalresearchnetwork.us/index.php/ajshr

The Impact of FGFR4 Gene SNP (Rs 1966265) on the Progression of Colorectal Cancer in Some Iraqi Patients

Hayder Mazin Alhaboobi[1], Hamsa Ahmed Jasim[1], Susan Zwya[2]

[1] University of Baghdad, Institute of Genetic Engineering and Biotechnology for Post Graduate
[2] College of Health and Medical Technology, Middle Technical University

Abstract:
The high death and prevalence risk of colorectal cancer (CRC) continue to be a worldwide health consequence due to its complex nature. The protein receptor fibroblast expansion element 4 with the aberrant regulatory sequences it activates have been found to have a significant impact on cancer formation and survival. The purpose of this research was to examine the role of FGFR4 genetic polymorphisms in CRC formation and progression. Fifty colorectal cancer cases and fifty non-cancerous controls were analyzed for the FGFR4 SNP. Neither the case nor the control groups showed any discernible SNP-related increase in Cancer risk. Participants with rectal cancer who have at minimum one small mutation of rs1966265 (AG and GG; AOR, 0.256; p = 0.36) become more likely to acquire metastases likened to those with heterozygous for the main allele.

Keywords: colorectal cancer; single-nucleotide polymorphism.

1. Introduction

Of the largest prevalent types of cancer, colorectal cancer (CRC) ranks first in men and is a leading contributor of cancer mortality globally [1]. The age-adjusted death rate from CRC in Iraq has risen even as surgical and alternative therapies have improved [2]. Diet and chronic exposures to disease chemicals, including cigarette usage drinking habits, have been identified as key environmental factors of CRC [3]. It has also shown that a wide variety of genetic changes that affect autophagy, adherence, vasculature, and proliferation and differentiation cause colorectal carcinogenesis [4]. The dysbiosis of intestinal microbiota at the junction of the aforementioned vulnerability variables has recently become a key predictor of CRC pathogenesis [5], in additional to hosting characteristics. Every one of these illnesses seem to be linked therefore required to estimate the cancer recognizing the considerable variability in CRC etiology [6].

Citation: Alhaboobi, H. M., Jasim, H. A., & Zwya, S. (2024). The Impact of FGFR4 Gene SNP (Rs 1966265) on the Progression of Colorectal Cancer in Some Iraqi Patients. American Journal of Social and Humanitarian Research, 5(6), 37–41. Retrieved from https://globalresearchnetwork.us/index.php/ajshr/article/view/2807

Received: 21 April 2024
Revised: 29 April 2024
Accepted: 20 May 2024
Published: 08 Jun 2024

And including FGFR1–3, fibroblast growth factor receptor 4 (FGFR4) is a member of a capsid group of hydrophobic mtorc1. The members of this group have been shown to coordinate carcinogenic transmission in different cancers, namely in the processes of revascularization and epidermis transformation (EMT) [7]. Abnormal FGFR4 action, like that of others FGFR close relatives, has been associated to the development of malignancies, particularly in cases of FGF19 overexpression [8]. Interconnected evidence suggests that deregulation of FGFR4 upstream kinases such Wnt/ -catenin [9], JAK/STAT [10], and PI3K-AKT [11] results in increased cellular proliferation as well as the propensity for metastasis in the development of cancer. Heads and collar [12,13], lung [14], prostrate [15-17], mammary [18,19], intestine [20], peritoneal [21], and uterus ovarian [22] cancers are only some of the many forms of cancer for which studies have shown FGFR4 nucleotide mutations to be associated with danger, prognostic, or response to therapy.

2. Materials and Methods

2.1. Subjects

Individuals were included between 2016 and 2020, and included 50 people with CRC and 50 healthy volunteers. All respondents received their formal contract before being enrolled in the trial. Diagnostic screening of individuals suffering from CRC was performed using the AJCC Staging system method [23]. A pathology evaluated the tumor for differentiating and assigned a grade based on the AJCC's criteria[24]. Participants with no need for an identity cancer diagnosis of any location were also excluded from enrollment in the healthy controls, were therefore those with asthmatic, hypertension, cardiology, neurodegenerative, or immunological illnesses. In order to have a better understanding of the population, we acquired participants' ages and sexes [25].

2.2. Genotyping

About 3ml of blood sample from each patient and healthy subjects have been collected in EDTA tube and then kept under -30 C until the time of work. Genomic DNA was isolated from the blood samples using commercial kit (mini-prep ZYMO research, USA) then electrophoresis have been done in order to detect the isolation process by running 5 µl of DNA through 2% agaros gel and stained with RedSafe (Intron, Korea), the gel have been subjected to 90 voltage for 45 minutes. In order to genotype rs1966265 SNP, a specific region of the FGFR4 gene that contain the desired SNP have been amplified by using RT – PCR .

2.3. Statistical Analysis

Using statistical analysis programs, the data from this research was assembled into distributed and Statistics descriptions, the automated data folder, and measures of dispersion (SPSS). Probabilistic below 0.01 (p0.01) was utilized in both the Sign Differences (LSD) test and the statistics of variances (ANOVA) testing.

3. Results

3.1. The distributions of controls and patients with CRC according to age and gender .The characteristic of the patients and control are summarized in table (3-1) the number of male/female at patient group 30/20 respectively and the ratio of male/female were (60%)/(40%) while for control group were .

the age of patients group which less than 65 years were (44.3%) while more than (55.7).and the age of control group less than 65 years were (47.0%) and mor than 65 years were (53.0%).

variable	Control (N=50) N%	Patients(N=50) N%
male	31(62.5%)	30(60%)
female	19(37.5%)	20(40%)
More than 65 years	27(53%)	28(55.7)
Less than 65years	32(47%)	22(44.3)

3.2. Association of FGFR4 Gene Polymorphism with the Progression of CRC

The rs1966265 single-nucleotide polymorphism (SNP) of the FGFR4 genome was chosen to investigate the possible impact of FGFR4 single nucleotide polymorphisms on CRC advancement because of its widespread connections with the onset of other cancers [13,14,16,27]. Our cohort's gene frequency counts also analyzed (Table 2). No statistically significant association of this FGFR4 mutation and CRC incidence was found when comparing cases and controls. Our research has shown that individuals with rectal cancer who had at least one polymorphism variant of two nucleotide SNPs (AG & GG for rs1966; AOR, 0.23; 95% CI, 0.05-0.97; p = 0.04) have a reduced risk of developing the disease. These results suggest a protective effect of a variation in the FGFR4 locus on the ability of rectal tumors to metastasize.

Table 2. Genotype distributions of FGFR4 gene polymorphism controls and patient

Variable	Control (N=50) N%	Patient (N=50) N%	OR(95% IC)
rs1966265			
AA	12(24.0%)	14.5(29.5%)	
AG	26(51.3%)	23(46.5%)	
GG	12(24.7)	12.5(24.0%)	
AG +GG	38(76.0%)	51(70.5%)	

4. Discussion

The development of CRC is a complicated process governed by both environmental and genetic variables, as has become evident from the available research. According to our findings, the rs1966265 variant in the FGFR4 gene mediates CRC's tumor progression but does not increase the risk of developing colonic malignancy. Another nonsense SNP, rs1966265, was identified in our analysis as being linked to CRC metastases. When the A allele replaces the G allele, the receptor's amino - terminal shifts from gene that codes to isoleucine at location. Combining this FGFR4 SNP with just another mutated gene has already been linked intestinal absorption balance to gastrointestinal passage in IBS severe vomiting [32]. This bile salt axis is thought to play a crucial role in gastrointestinal tumorigenesis [33], since bile acid deficiency alters the makeup of microorganisms in the colon environment in additional to host tissue [34]. The chance of getting malignancy, in addition to stomach malignancies, has been linked to rs1966265 [35]. Thus, we observed that having one minor variant of rs1966265 reduced the risk of metastatic in individuals with hematological malignancies, versus having both major alleles. . In conclusion, we show that the FGFR4 SNP rs1966265 is linked to increased risk of metastasis in advanced disease. These results highlight a hitherto unrecognized genetic correlation involving FGFR4 variation and CRC advancement, indicating that individuals with a certain Gene may have more rapid tumor growth than those with other Genotypes.

References

1. Sung, H.; Ferlay, J.; Siegel, R.L.; Laversanne, M.; Soerjomataram, I.; Jemal, A.; Bray, F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J. Clin. **2021**, 71, 209–249. [CrossRef] [PubMed]

2. Kuo, C.N.; Liao, Y.M.; Kuo, L.N.; Tsai, H.J.; Chang, W.C.; Yen, Y. Cancers in Taiwan: Practical insight from epidemiology, treatments, biomarkers, and cost. J. Formos. Med. Assoc. **2020**, 119, 1731–1741. [CrossRef] [PubMed]

3. Su, S.Y.; Huang, J.Y.; Jian, Z.H.; Ho, C.C.; Lung, C.C.; Liaw, Y.P. Mortality of colorectal cancer in Taiwan, 1971-2010: Temporal changes and age-period-cohort analysis. Int. J. Colorectal Dis. **2012**, 27, 1665–1672. [CrossRef] [PubMed]

4. Hull, R.; Francies, F.Z.; Oyomno, M.; Dlamini, Z. Colorectal Cancer Genetics, Incidence and Risk Factors: In Search for Targeted Therapies. Cancer Manag. Res. **2020**, 12, 9869–9882. [CrossRef] [PubMed]

5. Takayama, T.; Miyanishi, K.; Hayashi, T.; Sato, Y.; Niitsu, Y. Colorectal cancer: Genetics of development and metastasis. J. Gastroenterol. **2006**, 41, 185–192. [CrossRef] [PubMed]

6. Brennan, C.A.; Garrett, W.S. Gut Microbiota, Inflammation, and Colorectal Cancer. Annu. Rev. Microbiol. **2016**, 70, 395–411. [CrossRef]

7. Babina, I.S.; Turner, N.C. Advances and challenges in targeting FGFR signalling in cancer. Nat. Rev. Cancer **2017**, 17, 318–332. [CrossRef]

8. Liu, Y.; Cao, M.; Cai, Y.; Li, X.; Zhao, C.; Cui, R. Dissecting the Role of the FGF19-FGFR4 Signaling Pathway in Cancer Development and Progression. Front. Cell Dev. Biol. **2020**, 8, 95. [CrossRef]

9. Pai, R.; Dunlap, D.; Qing, J.; Mohtashemi, I.; Hotzel, K.; French, D.M. Inhibition of fibroblast growth factor 19 reduces tumor growth by modulating beta-catenin signaling. Cancer Res. **2008**, 68, 5086–5095. [CrossRef]

10. Hart, K.C.; Robertson, S.C.; Kanemitsu, M.Y.; Meyer, A.N.; Tynan, J.A.; Donoghue, D.J. Transformation and Stat activation by derivatives of FGFR1, FGFR3, and FGFR4. Oncogene **2000**, 19, 3309–3320. [CrossRef]

11. Touat, M.; Ileana, E.; Postel-Vinay, S.; Andre, F.; Soria, J.C. Targeting FGFR Signaling in Cancer. Clin. Cancer Res. **2015**, 21, 2684–2694. [CrossRef]

12. Farnebo, L.; Tiefenbock, K.; Ansell, A.; Thunell, L.K.; Garvin, S.; Roberg, K. Strong expression of survivin is associated with positive response to radiotherapy and improved overall survival in head and neck squamous cell carcinoma patients. Int. J. Cancer **2013**, 133, 1994–2003. [CrossRef] [PubMed]

13. Chou, C.H.; Hsieh, M.J.; Chuang, C.Y.; Lin, J.T.; Yeh, C.M.; Tseng, P.Y.; Yang, S.F.; Chen, M.K.; Lin, C.W. Functional FGFR4 Gly388Arg polymorphism contributes to oral squamous cell carcinoma susceptibility. Oncotarget **2017**, 8, 96225–96238. [CrossRef] [PubMed]

14. Li, J.P.; Huang, H.C.; Yang, P.J.; Chang, C.Y.; Chao, Y.H.; Tsao, T.C.; Huang, H.; Hung, Y.C.; Hsieh, M.J.; Yang, S.F. FGFR4 Gene Polymorphism Reduces the Risk of Distant Metastasis in Lung Adenocarcinoma in Taiwan. Int. J. Environ. Res. Public Health **2020**, 17, 5694. [CrossRef] [PubMed]

15. Ma, Z.; Tsuchiya, N.; Yuasa, T.; Inoue, T.; Kumazawa, T.; Narita, S.; Horikawa, Y.; Tsuruta, H.; Obara, T.; Saito, M.; et al.

16. Polymorphisms of fibroblast growth factor receptor 4 have association with the development of prostate cancer and benign prostatic hyperplasia and the progression of prostate cancer in a Japanese population. Int. J. Cancer **2008**, 123, 2574–2579.

17. Wang, J.; Stockton, D.W.; Ittmann, M. The fibroblast growth factor receptor-4 Arg388 allele is associated with prostate cancer initiation and progression. Clin. Cancer Res. **2004**, 10, 6169–6178. [CrossRef]

18. Marme, F.; Werft, W.; Benner, A.; Burwinkel, B.; Sinn, P.; Sohn, C.; Lichter, P.; Hahn, M.; Schneeweiss, A. FGFR4 Arg388 genotype is associated with pathological complete response to neoadjuvant chemotherapy for primary breast cancer. Ann. Oncol. **2010**, 21, 1636–1642. [CrossRef]

19. Bange, J.; Prechtl, D.; Cheburkin, Y.; Specht, K.; Harbeck, N.; Schmitt, M.; Knyazeva, T.; Muller, S.; Gartner, S.; Sures, I.; et al. Cancer progression and tumor cell motility are associated with the FGFR4 Arg(388) allele. Cancer Res. **2002**, 62, 840–847.

20. Marme, F.; Hielscher, T.; Hug, S.; Bondong, S.; Zeillinger, R.; Castillo-Tong, D.C.; Sehouli, J.; Braicu, I.; Vergote, I.; Isabella, C.; et al. Fibroblast growth factor receptor 4 gene (FGFR4) 388Arg allele predicts prolonged survival and platinum sensitivity in advanced ovarian cancer. Int. J. Cancer **2012**, 131, E586–E591. [CrossRef]

21. Yang, Y.; Zhou, Y.; Lu, M.; An, Y.; Li, R.; Chen, Y.; Lu, D.R.; Jin, L.; Zhou, W.P.; Qian, J.; et al. Association between fibroblast growth factor receptor 4 polymorphisms and risk of hepatocellular carcinoma. Mol. Carcinog. **2012**, 51, 515–521. [CrossRef]

22. Chen, T.H.; Yang, S.F.; Liu, Y.F.; Lin, W.L.; Han, C.P.; Wang, P.H. Association of Fibroblast Growth Factor Receptor 4 Genetic Polymorphisms With the Development of Uterine Cervical Cancer and Patient Prognosis. Reprod. Sci. **2018**, 25, 86–93. [CrossRef]

23. Edge, S.B.; Compton, C.C. The American Joint Committee on Cancer: The 7th edition of the AJCC cancer staging manual and the future of TNM. Ann. Surg. Oncol. **2010**, 17, 1471–1474. [CrossRef] [PubMed]

24. Tsay, M.D.; Hsieh, M.J.; Lee, C.Y.;Wang, S.S.; Chen, C.S.; Hung, S.C.; Lin, C.Y.; Yang, S.F. Involvement of FGFR4 Gene Variants on the Clinicopathological Severity in Urothelial Cell Carcinoma. Int. J. Environ. Res. Public Health **2019**, 17, 129. [CrossRef]

25. Wong, B.S.; Camilleri, M.; Carlson, P.J.; Guicciardi, M.E.; Burton, D.; McKinzie, S.; Rao, A.S.; Zinsmeister, A.R.; Gores, G.J. A Klothobeta variant mediates protein stability and associates with colon transit in irritable bowel syndrome with diarrhea. Gastroenterology **2011**, 140, 1934–1942. [CrossRef] [PubMed]

26. Ajouz, H.; Mukherji, D.; Shamseddine, A. Secondary bile acids: An underrecognized cause of colon cancer. World J. Surg. Oncol. **2014**, 12, 164. [CrossRef] [PubMed]

27. Liu, T.; Song, X.; Khan, S.; Li, Y.; Guo, Z.; Li, C.; Wang, S.; Dong, W.; Liu, W.; Wang, B.; et al. The gut microbiota at the intersection of bile acids and intestinal carcinogenesis: An old story, yet mesmerizing. Int. J. Cancer **2020**, 146, 1780–1790. [CrossRef]

28. Jiang, Y.; Sun, S.;Wei, W.; Ren, Y.; Liu, J.; Pang, D. Association of FGFR3 and FGFR4 gene polymorphisms with breast cancer in Chinese women of Heilongjiang province. Oncotarget **2015**, 6, 34023–34029. [CrossRef]