https://doi.org/10.31351/vol34iss1pp26-34

# Impact of XPD Lys751Gln Genetic Polymorphism on Oxaliplatin-Based Regimen Induced Toxicities in Iraqi Colorectal Cancer Patients

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Received 9/8/2023, Accepted 29/11/2023, Published 29/3/2025



## Abstract

The XPD Lys751Gln polymorphism may affect individual differences in DNA repair ability, which could increase a person's risk of developing toxicities when receiving oxaliplatin containing regimen in colorectal cancer patients (CRC). Therefore, assessment of XPD Lys751Gln polymorphism may generate crucial data for identifying individuals at high risk for serious adverse effects and thus choosing the best treatment option. Hence the aim of the current research is to find out the association between XPD Lys751Gln polymorphism and oxaliplatin-based regimen toxicities among a sample of Iraqi population with CRC. Seventy-two CRC patients on oxaliplatin-based regimen were enrolled in the study and were followed for 4 cycles. Polymerase chain reaction (PCR) was used for genotyping, followed by sequencing. Toxicities were recorded before the start of each of the four cycles then the relationship between this SNP and observed toxicities was examined. There was no significant association between Lysn751 Gln genotypes and studied hematological and non-hematological toxicities. Taken together, The XPD Lys751Gln polymorphism cannot be considered a potential biomarker for platinum induced toxicity.

**Keywords: Colorectal carcinoma; Lys751Gln; Oxaliplatin; rs13181**

## Introduction

One of the most frequent malignancies is colorectal cancer (CRC), which was diagnosed in 2 million people in the year 2020, ranking third most common among all cancers in the world [(1)]. Similarly, according to the recent figures in Iraq, there were 2,328 new cases in 2019 making it the third most frequent cancer among Iraqi population [(2)]. CRC carcinogenesis follows one of three molecular pathways: microsatellite instability, chromosomal instability and Cytosine guanine (CpG) island methylator phenotype [(3, 4)].

While the majority of CRC cases are diagnosed among patients aged 50 years and older; recently, CRC cases are reported at younger age [(5)]. In a number of cases, CRC start as extremely small, asymptomatic polyps, and patients may not exhibit any symptom in the early stages of the disease. When symptoms do appear, they vary depending on the location of the tumor, whether lymph nodes are involved, and whether it has spread to other organs [(6, 7)].

Treatment of colorectal cancer has advanced significantly over time. Recently, oxaliplatin has been added to several pre-existing regimens as adjuvant, neoadjuvant as well as palliative therapy [(8)]. Oxaliplatin is a platinum derivative that acts through generation of bulky DNA adducts as a result of intra-strand DNA cross-linking by binding to purine bases. In addition, it hinders DNA repair mechanisms leading to accelerated apoptosis rate [(9)]. It is usually given either with 5-florouracil and leucovorin as FOLFOX regimen or with capecitabine which is an oral prodrug of 5-florouracil as CAPOX [(10)]. FOLFOX regimen consists of 85 mg/m$^2$ oxaliplatin IV plus 400 mg/m$^2$ Leucovorin and 5-florouracil 400 mg/m$^2$ bolus on day 1 followed by 2400 mg/m$^2$ as a 46-h infusion. The cycle is given every 2 weeks for 24 weeks [(11)]. Whereas CAPOX is given as oxaliplatin 130 mg/m$^2$ IV on day 1 and capecitabine 1000mg/m$^2$ twice daily orally from day 1 until day 14 and each cycle lasts 3 weeks[(12)].

A considerable number of patients encounter severe toxicity at some time during their therapy, which frequently results in dose reductions, chemotherapy cycles delay, and even treatment cessation in many patients which results in reduced efficacy [(13)]. This interindividual variation in the degree of chemotherapy adverse effects is due to

several factors, one of them is genetic polymorphisms in genes involved in the pathway of the utilized chemotherapy agents [14]. One of the crucial genes that have been studied with the clinical outcome of oxaliplatin based therapy is Xeroderma Pigmentosum group D (*XPD*) gene which is also Known as Excision Repair Cross-Complementing Group 2 (*ERCC2*) [15].Its location is at chromosome 19q13.3 and consists of 23 exons which span around ~54.3 kb in length; the enzyme encoded by this gene is part of ATP-dependent 5′-3′ superfamily 2 helicases which plays a critical role in nucleotide excision repair pathway [16]. Of the extensively studied polymorphisms of *XPD* gene in relation to oxaliplatin is rs13181 which corresponds to substitution of lysine by glutamine at codon 751 due to conversion of adenine to cytosine at exon 23 (Lys751Gln) [17]. The previously mentioned single nucleotide polymorphism (SNP) is associated with lower DNA repair capacity. Meanwhile the bulky DNA adducts produced by oxaliplatin is thought to be fixed by NER pathway. Therefore, Lys751Gln variant leads to increased oxaliplatin cellular damage even in normal cells and increases the level of toxicity [18].

Several researchers have explored the potential impact of Lys751Gln on toxicity caused oxaliplatin-based therapy in CRC patients; Gul *et al* found that homozygous variant in CRC patients showed 11 times raised incidence of grade 3 to 4 hematologic toxicity. In addition, non-hematologic adverse effects are 13 folds more likely to occur than patients with wild homozygous genotype [19]. In a study done on Italian CRC patients receiving either CAPOX or FOLFOX, C allele was associated with increased risk of hematological toxicity [20].

Kjersem *et al* conducted a study on CRC patients from multiple Nordic centers and showed that individuals with TT genotype are more prone to suffer from nausea at any grade in comparison with patients with G allele [21]. Given that FOLFOX and CAPOX regimens are highly utilized in the treatment of CRC, patients still suffer from adverse effects that may last even after termination of chemotherapy cycles [22]. In that sense, identifying SNPs that could serve as a predictive biomarker for susceptible individuals can lead to improvement in the quality of life of those patients through implementing therapeutic protocols (by reducing the dose or even choosing another regimen) [23].

We aimed at illuminating the influence of Lys751Gln on toxicity of oxaliplatin based regimen among a sample of Iraqi CRC patients

## Materials and Methods

### *Study subjects*

This is an observational prospective cohort study which included a convenient sample of 72 CRC patients who were recruited from Oncology Teaching Hospital- Medical city/ Baghdad from February to December 2022. Inclusion criteria included adult patients with confirmed CRC diagnosis who are receiving CAPOX regimen. Exclusion criteria included patients who have or had other types of cancers, patients with neurological or genetic diseases and patients who have less than four cycles left. This study was performed in line with the principles of the Declaration of Helsinki [24]. Approval was granted by the Ethics Committee of Baghdad University/ College of Pharmacy (approval number: RECAUBCP26102021B on 26-10-2021). All subjects provided their consent to participate. By performing a colonoscopy and a histopathological biopsy, the CRC diagnosis was verified [25]. The American Joint Committee on Cancer (AJCC) staging classification system was used for CRC staging [26]. A questionnaire was used to collect demographics, clinical data and toxicity-related information.

### *Toxicity evaluation*

Patients were followed for four cycles and treatment related toxicity was recorded before each cycle and graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 5 published by national cancer institute [27]. Common adverse events related to CAPOX regimen were assessed which includes hematological toxicities (anemia, thrombocytopenia, leucopenia, neutropenia) and non-hematologic toxicities (fatigue, peripheral neuropathy, laryngopharyngeal dysesthesia hand-foot syndrome, nausea, vomiting and diarrhea).

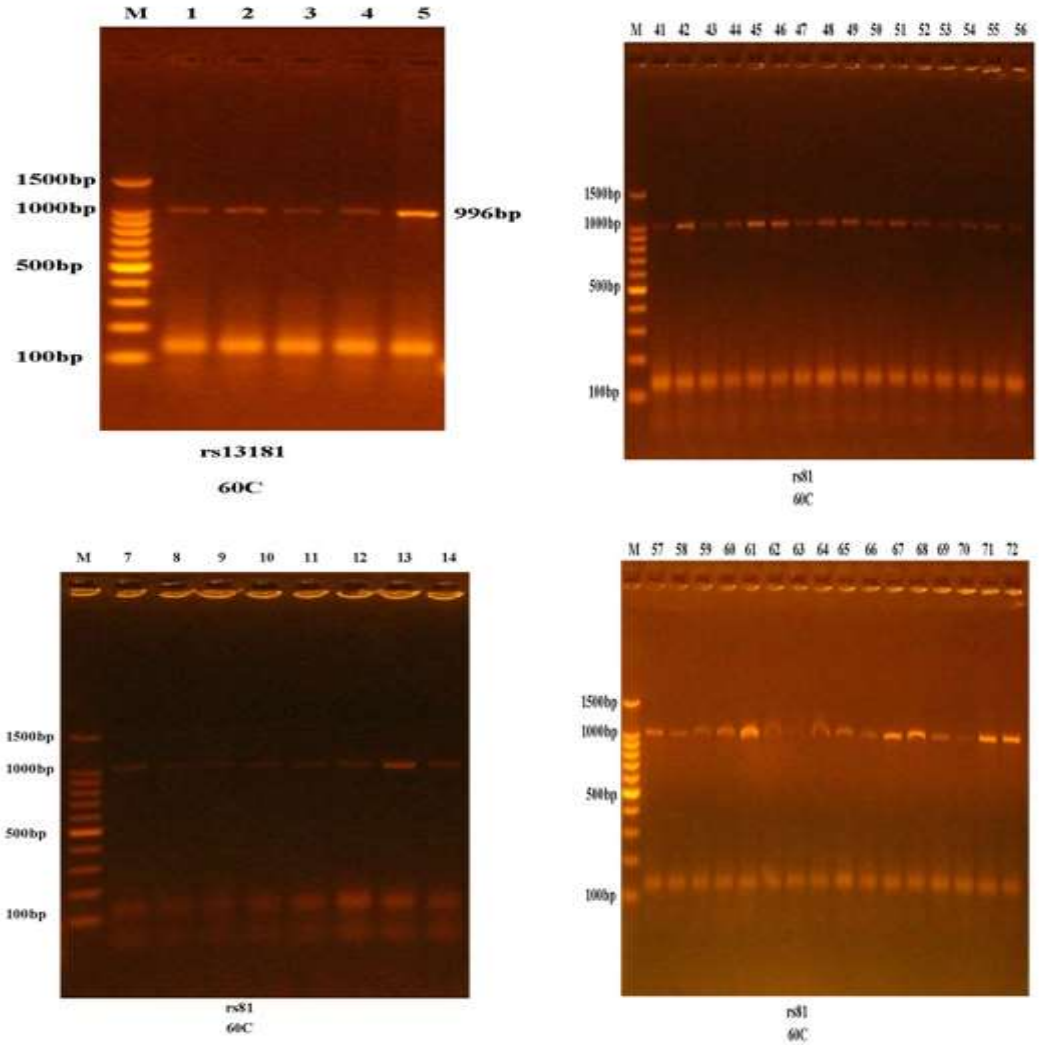
### *DNA extraction and Genotyping*

Three millimeters of venous blood were drawn from every patient in K3EDTA-coated tubes, and DNA was extracted using the ReliaPrepTM Blood gDNA Miniprep System (Promega, USA) in accordance with the manufacturer's recommendations. Quantus Fluorometer was used to identify the concentration and quality of the extracted DNA. The GenBank database of the National Center for Biotechnology Information (NCBI) was utilized for the DNA sequence to be amplified. XPD primers were created using Premier 3 software (version 0.4.0). Primers' length, annealing temperature and amplicon size are illustrated in Table 1. After designing the primers, 5`end for each forward and reverse primers were tailed with M13 sequence of base pairs for the purpose of sequencing. PCR technique was conducted using a thermal cycler (Thermo Fisher Scientific, USA).

**Table 1. Primer's characteristics.**

| Primer Name | Sequence | Primer length | Annealing Temp. (˚C) | Productsize (bp) |
|---|---|---|---|---|
| Forward | TGTAAAACGACGGCCAGTCCCTCAGCAAAG AGAAGTTTA | 39 | 60 | 996 |
| Reverse | CAGGAAACAGCTATGACCAGGACAGGA GCAAAGATG | 36 | | |

Agarose gel electrophoresis was used to find PCR products and confirm amplification. PCR amplicons are shown in Figure 1. The data were then analyzed by genius software (V 2021.1.1) (Biomatters Ltd., Auckland, New Zealand; www.geneious.com) after the PCR amplicons were delivered to Macrogen Corporation - Korea for Sanger sequencing utilizing an automated DNA sequencer




.**Figure 1. Results of the amplification of rs13181 on 1.5% agarose gel stained with Ethidium Bromide. M: 100bp ladder marker.**

***Statistical analysis***

Data were analyzed using SPSS software version 26 (SPSS® Inc, Chicago, USA). Categorical variables were expressed as N (%) whereas continuous data were expressed as mean ± Standard deviation (SD). Demographic and clinical data were compared using Student t- test, chi square or fisher exact test as appropriate. Toxicity was expressed as dichotomous variable (toxicity vs. no toxicity) and strength of association with genetic polymorphism

was examined using odds ratio (OR) with 95% confidence interval. p-value <0.05 was considered statically significant.

## Results

***Patients' characteristics***

The present study included 72 CRC patients. Their average age is 56.3 ± 11.88 years with a range of (26-81) years. Male to female ratio is 1.3:1. Regarding smoking-status, 44.4% of patients are smokers. The majority of patients had their tumor in the colon (70.8%) and most tumors are moderately differentiated (61.1%). Other patient characteristics and malignancy related data are illustrated in Table (2). Distribution of genotypes according to gender and age was analyzed to ensure internal validity and no statistically significant differentiation was found.

***Genotype and allele distribution***

The most frequent genotype was TT with a percentage of 43.06% (31 out of 72) and the least common genotype was GG 23.61% (17 out of 72). G allele was the minor allele with a percentage of 40.28%. Table (3) shows genotype and MAF frequencies.

**Table 2. Patients' demographics and clinical characteristics**

| **Parameters** | **N (%) or mean ± SD** |
|---|---|
| Age (years) | 56.3 ± 11.88 |
| Gender | |
| Male | 41 (56.9%) |
| female | 31 (43.1%) |
| Smoking | |
| Yes | 32 (44.4%) |
| No | 40 (55.6%) |
| BMI ($Kg/m^2$) | 26.14 ±4.039 |
| Tumor location | |
| Colon | 51 (70.8%) |
| rectum | 21 (29.2%) |
| Tumor differentiation | |
| Well | 13 (18.1%) |
| Moderate | 44 (61.1%) |
| poor | 15 (20.8%) |
| Stage | |
| II | 31 (43.1%) |
| III | 29 (40.3%) |
| IV | 12 (16.7%) |
| Tumor invasion | |
| T1 and T2 | 12 (16.7%) |
| T3 and T4 | 60 (83.3%) |
| Lymph node involvement | |
| Yes | 43 (59.7%) |
| No | 29 (40.3%) |
| Metastasis | |
| Yes | 12 (16.7%) |
| No | 60 (83.3%) |

BMI: Body Mass Index.

**Table 3. Genotypes and allele frequencies**

| Genotypes | N (%) |
|---|---|
| TT | 31(43.06%) |
| TG | 24(33.33%) |
| GG | 17(23.61%) |
| MAF | 58(40.28%) |

MAF: Minimum allele frequency, minor allele is G

***Treatment related toxicities and association with genetic polymorphisms***

The most prevalent hematological toxicity observed was leucopenia (19%). On the other hand, the least common was anemia (19.4%). Regarding non-hematological toxicities, peripheral neuropathy and nausea had the highest frequency with an equal percentage of 52.8% while the least frequent toxicity was hepatotoxicity (represented by raised liver enzymes with a percentage of 12.5%). Other toxicities are demonstrated in Table (4).

**Table 4. Observed toxicities in patients receiving CAPOX therapy**

| **Toxicity** | **N (%)** |
|---|---|
| Hematological toxicities | |
| Anemia | 14 (19.4%) |
| Thrombocytopenia | 15 (20.8%) |
| Leucopenia | 23 (19%) |
| Neutropenia | 22 (30.6%) |
| Non-hematological toxicities | |
| Peripheral neuropathy | 38 (52.8%) |
| Laryngopharyngeal dysesthesia | 12 (16.7%) |
| Diarrhea | 19 (26.4%) |
| Nausea / vomiting | 57 (79.6%) |
| Elevated aminotransferases levels | 9 (12.5%) |
| Renal toxicity | 10 (13.9%) |
| Hand-foot syndrome | 15 (19.2%) |
| Fatigue | 39 (50%) |

There was lack of association between Lys751Gln genotypes with hematologic and non-hematologic toxicities as demonstrated in Tables 5 and 6

**Table 5. Association of Lys751 Gln with CAPOX induced hematologic toxicities**

| Genotype | Anemia | | p-value |
|---|---|---|---|
| | **Yes N= (%)** | **No N=58 (%)** | |
| TT | 4 (28.6%) | 27 (46.6%) | Reference |
| GT | 5 (35.7%) | 19 (32.8%) | 0.48 [b] |
| GG | 5 (35.7%) | 12 (20.7%) | 0.24 [b] |
| Thrombocytopenia | | | |
| | Yes N= (%) | No N= 57 (%) | |
| TT | 4 (26.7%) | 27 (47.7%) | Reference |
| GT | 7 (46.7%) | 17 (29.8%) | 0.18 [b] |
| GG | 4 (26.7%) | 13 (22.8%) | 0.42 [b] |
| Leucopenia | | | |
| | Yes N=23 (%) | No N=49 (%) | |
| TT | 9 (39.1%) | 22 (44.9%) | Reference |
| GT | 9 (39.1%) | 15 (30.6%) | 0.50 [a] |
| GG | 5 (21.8%) | 12 (24.5%) | 0.97 [a] |
| Neutropenia | | | |
| | Yes N= (%) | No N=50 (%) | |
| TT | 13 (59.1%) | 18 (36%) | Reference |
| GT | 6 (27.3%) | 18 (36%) | 0.19 [a] |
| GG | 3 (13.6%) | 14 (28%) | 0.11 [b] |

[a] chi square was used, [b] Fisher exact test was used, TT is the wild genotype

**Table 6.Association of Lys751 Gln with CAPOX induced non-hematologic toxicities**

| Genotype | Peripheral neuropathy | | p-value |
|---|---|---|---|
| | Yes N=(%) | No N=34 (%) | |
| TT | 17 (44.7%) | 14 (41.2%) | Reference |
| GT | 10 (26.3%) | 14 (41.2%) | 0.33 [a] |

| | | | |
|---|---|---|---|
| GG | 11 (28.9%) | 6 (17.6%) | 0.50 [a] |
| Laryngopharyngeal dysesthesia | | | |
| | Yes N=12 (%) | No N=60 (%) | |
| TT | 7 (58.4%) | 24 (40%) | Reference |
| GT | 1 (8.3%) | 23 (38.3%) | 0.11 [b] |
| GG | 4 (33.3%) | 13 (21.7%) | 1 [b] |
| Hepatotoxicity | | | |
| | Yes N=9 (%) | No N=63 (%) | |
| TT | 2 (22.2%) | 29 (46%) | Reference |
| GT | 5 (55.6%) | 19 (30.2%) | 0.22 [b] |
| GG | 2 (22.2%) | 15 (23.8%) | 0.60 [b] |
| Renal toxicity | | | |
| | Yes N=10 (%) | No N=62 (%) | |
| TT | 4 (40%) | 27 (43.5%) | Reference |
| GT | 4 (40%) | 20 (32.3%) | 0.70 [b] |
| GG | 2 (20%) | 15 (24.2%) | 1 [b] |
| Hand foot syndrome | | | |
| | Yes N=(%) | No N=58 (%) | |
| TT | 6 (42.9%) | 25 (43.1%) | Reference |
| GT | 4 (28.6%) | 20 (34.5%) | 1 [b] |
| GG | 4 (28.6%) | 13 (22.4%) | 0.72 [b] |
| Fatigue | | | |
| | Yes N=(%) | No N=38 (%) | |
| TT | 15 (44.1%) | 16 (42.1%) | Reference |
| GT | 9 (26.5%) | 15 (39.5%) | 0.41 [a] |
| GG | 10 (29.4%) | 7 (18.4%) | 0.48 [a] |
| Nausea/vomiting | | | |
| | Yes N=(%) | No N=15 (%) | |
| TT | 24 (42.1%) | 7 (46.6%) | Reference |
| GT | 20 (35.1%) | 4 (26.7%) | 0.73 [b] |
| GG | 13 (22.8%) | 4 (26.7%) | 1 [b] |
| Diarrhea | | | |
| | Yes N=(%) | No N=53 (%) | |
| TT | 8 (42.1%) | 23 (43.4%) | Reference |
| GT | 6 (31.6%) | 18 (34%) | 0.94 [a] |
| GG | 5 (26.3%) | 12 (22.6%) | 0.78 [a] |

[a] chi square was used, [b] Fisher exact test was used, TT is the wild genotype

## Discussion

The current study explored the impact of Lys751Gln genetic polymorphism of *XPD* gene on toxicities observed in CRC patients receiving oxaliplatin based therapy. It revealed that there is no link between Lysn751Gln polymorphism and oxaliplatin based regimen toxicity. Since the introduction of oxaliplatin, oxaliplatin based regimens (FOLFOX and CAPOX) have been used as a first line agent in the management of colorectal cancer. However, oxaliplatin has been associated with serious adverse effects that made its utilization limited [(28)]. Hence, biomarkers that define who are the patients that will respond better to the selected regimen with minimal toxicity are needed.Pharmacogenetics are currently employed to personalize therapy and individualize strategies with the aim of therapeutic efficacy and safety promotion [(29)]. In the recent years there have been many attempts in Iraq to identify genetic markers for many malignancies as well as other serious diseases whose therapy may result in quality-of-life limitation [(30-35)]. Nonetheless, to the best of our knowledge, this is the first study in Iraq to assess the influence of *XPD* genetic polymorphisms on toxicity of CAPOX

regimen in CRC patients. The present research showed that neutropenia was the most frequent hematological toxicity whilst peripheral neuropathy and nausea was the most common non-hematological toxicities. In line with these results, Cecchin *et al* found that neutropenia was the most frequent adverse event in patients receiving FOLFOX regimen with a rate of 63.2%. In addition, nausea was the most common non-hematological toxicity with rate of 47.2% [28]. Moreover, an investigation was conducted on patients receiving FLOX regimen revealed that the most frequent non hematologic toxicity was sensory neuropathy (91.3%). However, the most common hematologic toxicity was thrombocytopenia (68.8%) [21]. Concerning the association of variant genotype with toxicity and in line with the current study, Cortejoso *et al*.'s investigation included Spanish CRC patients, of which 106 were being treated with an oxaliplatin-based regimen. None of the individuals had a significant relationship with the ERCC2 genetic variant [36]. Additionally, a study on rectal cancer patients conducted in the USA revealed that there was no statistically significant difference between the lys751gln genotypes in those patients who were receiving neoadjuvant chemotherapy that contained the FOLFOX regimen [37]. Moreover, a research comprised 316 rectal cancer patients 161 of them received CAPOX whilst 155 patients treated with capecitabine 800 mg/m2 twice daily; none of the treatment arms toxicities were associated with Lysn751Gln genotypes [38]. Furthermore, Spanish research was conducted to evaluate the effect of 8 polymorphisms in 6 genes including ERCC2 Lys751Gln on the clinical outcome of flurouracil-oxaliplatin regimen and concluded no association with hematological and non-hematological toxicities [39]On the contrary to the results of our study, in a research on Swedish CRC patients, Salimzadeh *et al*. found that carriers of at least one variant allele of rs13181 experienced ocular reaction, thrombocytopenia, and dosage reduction more frequently than carriers of the wild type genotype[40]. Besides, the incidence of grade 3 to 4 hematologic toxicity was more than 11 times higher in homozygous variant CRC patients in Pakistan compared to those with homozygous wild type genotype. In addition, patients with homozygous variant genotypes are more than 13 times more likely than patients with wild genotypes to experience non-hematologic adverse effects [19]. Patients with metastatic CRC who carry the C allele were linked to hematologic adverse events caused by FOLFOX but not neurologic or gastrointestinal adverse events, according to Boige *et al* [41].These inconsistent results could be explained by different ethnicities, various sample sizes, different oxaliplatin regimens used (FOLOX, FLOX, CAPOX) which means multiple doses of oxaliplatin and different number of cycles as some studies assessed the toxicities for 4 months [21], others followed the patients for 6 months [28].

Although the present research concluded lack of association between lys751gln *XPD* genetic polymorphism and oxaliplatin toxicity, there are some limitations in the study protocol which are relatively small sample size, single entered recruitment as well as the duration of the study as patients were followed for only 4 cycles hence further larger investigations should be performed taking into account the aforementioned limitations.

## Conclusion

The current study proposed lys751gln *XPD* genetic polymorphism may not be a good biomarker for predicting toxicity of oxaliplatin based regimen in CRC patients. Nonetheless, future studies with larger sample size, multicentered as well as longer duration of follow up are warranted to confirm the present research findings.

## Acknowledgment

The authors would like to express appreciation to all subjects whose participation made
this study possible.

## Conflicts of Interest

The authors declare no conflict of interest for this article.

## Funding

The authors declare that no funds, grants, or other support were received.

## Ethics Statements

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Baghdad University/ College of Pharmacy (approval number: RECAUBCP26102021B on 26-10-2021)

## Author Contribution

Study design (RF, ESS, AZA); conduct of study (RF); collection of data (RF); analysis, interpretation, and management of data (RF, ESS, AZA); preparation of manuscript (RF); intellectual content review (ESS, AZA); and approval of final manuscript draft (RF, ESS, AZA).

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# تقييم تأثير تعدد الاشكال الوراثية على السمية الناتجة من استخدام علاج Lys751Gln الاوكساليبلاتين لدى مرضى سرطان القولون والمستقيم

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**الخلاصة**

قد يؤثر تعدد الأشكال الوراثية XPD Lys751Gln على الاختلافات الفردية في قدرة إصلاح الحمض النووي، مما قد يزيد من خطر إصابة الشخص بالتسمم عند تلقي نظام يحتوي على أوكساليبلاتين في مرضى سرطان القولون والمستقيم. ولذلك، فإن تقييم تعدد الأشكال XPD Lys751Gln قد يولد بيانات مهمة لتحديد الأفراد المعرضين لخطر كبير للتأثيرات الضارة وبالتالي اختيار أفضل خيار علاجي. ومن هنا فإن الهدف من البحث الحالي هو معرفة العلاقة بين تعدد الأشكال الوراثية XPD Lys751Gln والاثار الجانبية للنظام المعتمد على الأوكساليبلاتين بين عينة من السكان العراقيين المصابين بسرطان القولون والمستقيم. تم تسجيل اثنين وسبعين مريضا من مرضى سرطان القولون والمستقيم على النظام القائم على أوكساليبلاتين في الدراسة وتمت متابعتهم لمدة ٤ دورات. تم استخدام تفاعل البوليميراز المتسلسل (PCR) في التنميط الجيني، يليه التسلسل الجيني. تم تسجيل الاثار الجانبية قبل بداية كل دورة من الدورات الأربع ثم تم فحص العلاقة بين تعدد الاشكال الوراثية والسمية المرصودة. لم يكن هناك ارتباط بين الأنماط الجينية Lysn751 Gln والاثار الجانبية الدموية وغير الدموية المدروسة ،لهذا لا يمكن اعتبار تعدد الأشكال XPD Lys751Gln علامة حيوية محتملة للسمية المستحثة بالاوكساليبلاتين.

**الكلمات المفتاحية : سرطان القولون والمستقيم ; لايسين ٧٥١ كلوتامين ; اوكساليبلاتين ; rs13181**