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Structural and Functional Analysis of DNA-repair Gene Variants (XRCC1, ERCC2/XPD) and their Relevance to Chronic Kidney Disease Pathogenesis

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ABSTRACT

Background: According to statistics, chronic kidney disease (CKD) is the fourth leading cause of death in the world and its rate of 4.32% of total deaths in Iraq. Over the past few years, several single -nucleotide polymorphisms (SNPs) have been recognized to be associated with increased risk for CKD.

Objectives: To computationally evaluate the impact of nonsynonymous single-nucleotide polymorphisms (nsSNPs) in the coding regions of the XRCC1 and XPD genes using multiple predictive tools.

Materials and methods: Several prediction methods and in silico theoretical models were used to examine non-synonymous SNPs in the XRCC1 and XPD genes. It has been demonstrated that the structure and function of the XRCC1 and XPD proteins, which are involved in deoxyribonucleic acid (DNA) repair, are affected by potentially harmful mutations rs25487, rs1799782, rs13181, and rs1799793.

Results: High-confidence three-dimensional structures of the human XRCC1 and XPD proteins were produced using the SWISS-MODEL platform. Mutant models with missense variations (rs25487, rs1799782, rs13181, and rs1799793) exhibited striking changes in protein stability and structure. Several variations have been shown to negatively impact protein function by in silico prediction techniques (i-Mutant, PolyPhen-2, PROVEAN, and SNPs and GO), with rs1799793 exhibiting the highest correlation with illness. The discussed polymorphisms appear to be highly relevant to DNA repair and genomic stability, a conclusion supported by additional analysis of protein–protein interactions, evolutionary conservation within and outside the species, as well as protein classification.

Conclusion: Our conclusion was that the rs1799793 variant impacted on the CKD. While the rs13181 polymorphism has shown protein stability increases, the others, including rs25487 and rs1799782 have shown decreases in their stability. Prediction tools (i-Mutant, PolyPhen-2, PROVEAN and SNPs&GO) indicated that XPD variants were generally benign, while the impact of XRCC1 variants could be deleterious.

Keywords: XRCC1; XPD; Nonsynonymous SNPs; SNP effect; Protein stability.

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INTRODUCTION

One of the major worldwide health concerns is chronic kidney disease (CKD) [1]. The phases of CKD are defined by a continual reduction in glomerular filtration rate (GFR), and comorbidities, including anemia and hyperparathyroidism often accompany the illness's development. One of the main causes of CKD is diabetes mellitus (DM). Diabetic kidney disease (DKD), a subgroup of CKD, is characterized by gradual renal deterioration and hypertension [2]. Pharmacological agents that directly influence on the renin-angiotensin-aldosterone system (RAAS) have been shown to be effective in slowing DKD progression [3]. Meanwhile, the prevalence of hypertension is increasing, particularly with ageing and obesity, which simultaneously increases the risk of CKD [4].

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Deoxyribonucleic acid (DNA) damage in renal cells can occur at the cellular level due to oxidative stress and inflammation. Base excision repair (BER) and nucleotide excision repair (NER), two important repair processes, are triggered in response [5]. Apoptosis, cellular senescence, and persistent pro-inflammatory signaling are triggered by the induction of p53 and the ATM/ATR pathway in response to acute DNA damage, which exacerbates tissue damage [6]. By causing transforming growth factor-β (TGF-β)-mediated fibrosis, persistent DNA damage responses contribute to the development of CKD [7, 8].

The XPD gene is situated at chromosome 19q13. 32 is essential for maintaining genomic integrity, particularly by mediating NER, which entails unwinding DNA during transcription and damage [9]. Variants of EBPs, such as Asp312Asn and Lys751Gln are associated with a reduced capacity for DNA repair, genomic instability and increased susceptibility to cancer [10, 11]. The Lys751Gln variant reduces helicase activity and is associated with aging-related disease and tumor susceptibility [12]. Moreover, extreme forms of photosensitivity like xeroderma pigmentosum (XP) also exhibit a strong association with defective DNA repair and hematological malignancies such as acute myeloid leukemia (AML) [13, 14].

However, the compromised resilience of renal tubular epithelial cells to oxidative and toxic injury is partially attributed to impaired DNA repair mechanisms [15]. This susceptibility promotes apoptosis, inflammation (cholesterol crystals), and cellular senescence, leading to interstitial fibrosis and nephron loss. Therefore, deficiency in DNA damage repair pathways is a major contributing factor towards CKD and its progression to end stage renal disease (ESRD) [16].

A second essential DNA repair gene, XRCC1, is located on chromosome 19q13. 31 in its capacity as a scaffold to recruit multiple enzymatic activities at multi-step DNA repair processes [17, 18]. Arg399Gln is one of the XRCC1 polymorphisms linked to an elevated risk of ESRD and other malignancies [19]. Research has shown that XRCC1 genetic variations may contribute to malignant conditions such as skin and esophageal cancer, the latter of which is associated with increased vulnerability [20] due to both genetic and environmental factors. Therefore, combinations of polymorphisms in the XRCC1 and XPD genes may be genetic markers of vulnerability to neurological disorders, cancer, and ESRD [21].

To enhance variant discovery and functional evaluation, recent developments in genomics have of increasing leveraged generative artificial intelligence (AI) techniques, including generative adversarial networks (GANs), variational autoencoders (VAEs), and big language models. By accurately simulating true genetic data and accurately predicting new variants, these methods, which are powered by AI powered methods, can greatly enhance the speed and precision of polymorphism analysis when used with bioinformatics' most popular tools, including GATK, PLINK or VCF-based tools.

This integrated paradigm facilitates the discovery of physiologically significant genetic variation in studies focused on populations and disease [22–24].

This study aims to predict nonsynonymous polymorphisms in the XRCC1 gene (Arg399Gln and Arg194Trp) and the XPD gene (Asp312Asn and Lys751Gln) in Iraqi patients with ESRD and to investigate any potential association between these polymorphisms and physiologically significant variations in the condition.

MATERIALS AND METHODS

The study was entirely computational and conducted at the Faculty of Science, University of Kufa. Ethical approval for the study was obtained from the MECC and the Najaf Health Directorate. The approval was granted in accordance with institutional regulations under form number 9695, dated March 13, 2025. The study covered the period from 14 March to 31 July 2025. Protein modeling is a computer method that uses an amino acid sequence to predict a protein's three-dimensional structure. Three-dimensional structures of the human XRCC1 and XPD proteins (P18887 and P18074-1), as annotated in UniProtKB/Swiss-Prot, were constructed. The key steps in protein modeling include:

A. **Sequence Acquisition:** The amino acid sequence of the target protein is obtained from the UniProt and Protein Data Bank (PDB) databases.
B. **Comparative Modeling:** The target protein sequence is aligned with homologous proteins whose three-dimensional structures have already been experimentally determined. The SWISS-MODEL server is commonly employed for this process.
C. **Model Refinement:** Following the generation of the initial structural model, molecular dynamics simulations and energy minimization techniques are applied to improve the accuracy and stability of the predicted structure.
D. **Validation:** Several computational tools are used to assess the quality and reliability of the generated protein model. In this study, I-TASSER was utilized for model validation, with submission identity numbers (ID) S777254 for XRCC1 and S875487 for XPD (https://aideepmed.com/I-TASSER/).
E. **Visualization:** The final three-dimensional (3D) protein model is visualized using YASARA software.
F. **Structural Analysis:** Predictions are performed to evaluate the potential effects of amino acid substitutions on protein structure and function.

To investigate the structural and functional consequences of the identified non-synonymous variants, namely rs25487 (T/C), rs1799782 (G/A), and rs1799793 (C/T), several bioinformatics platforms were employed, including dbSNP, I-Mutant v2.0, Polymorphism Phenotyping-2 (PolyPhen-2), Protein Variation Effect Analyzer (PROVEAN), Protein Analysis Through Evolutionary Relationships (PANTHER 19.0), and SNPs&GO. These tools were used to assess protein stability and predict the functional effects of the identified mutations. Only platforms with fully accessible web interfaces were included in the analysis.

A. PDB 101 (https://www.rcsb.org/): Provides access to experimentally determined three-dimensional protein structures. The PDB offers standardized deposition, validation, annotation, and dissemination of macromolecular structural data, ensuring data quality, consistent metadata, and global accessibility.
B. I-Mutant (https://folding.biofold.org/i-mutant/i-mutant2.0.html): Predicts the effects of point mutations on protein folding and stability. This tool estimates the impact of specific single nucleotide polymorphisms (SNPs) on protein stability by evaluating changes in Gibbs free energy (ΔG), thereby suggesting potential biological consequences.
C. PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/): Evaluates the potential functional impact of amino acid

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substitutions. PolyPhen-2 combines sequence-based information with protein structural features to classify nonsynonymous SNPs (nsSNPs) as benign, possibly damaging, or probably damaging.

D. SNPs&GO (https://snps.biofold.org/snps-and-go/snps-and-go.html): Identifies disease-associated SNPs through the analysis of protein properties and functional annotations. Gene Ontology (GO) terms are incorporated to describe the associated biological processes, molecular functions, and cellular components, thereby providing insights into DNA repair pathways and chronic kidney disease (CKD) pathophysiology.

E. PANTHER-PSEP 19.0 (https://pantherdb.org/): Predicts the functional effects of coding-region variations by evaluating the evolutionary conservation of amino acid residues. Amino acid substitutions occurring at highly conserved positions are more likely to be deleterious, whereas substitutions at less conserved sites are generally considered benign.

In the present study, YASARA (https://www.yasara.org/) was employed as a reliable platform for molecular modeling and visualization. The software provides advanced capabilities for molecular dynamics simulations and three-dimensional protein structure refinement. Such computational approaches are essential for understanding protein function, molecular interactions, and their involvement in pathological processes, with important applications in molecular biology and drug discovery. Figure **??** illustrates the complete workflow adopted for protein modeling and homology analysis.

Variants determined to be functionally relevant, specifically SNPs within coding sequences or regulatory regions were selected. Nonsynonymous SNPs, which could change protein structure or affect gene expression, were prioritized. Using resources such as dbSNP and ClinVar, we cross-referenced potentially functional SNPs with publicly available records of SNPs previously associated with disease. In silico predictive tools were subsequently employed to characterize the potential deleterious effects of these variants. Furthermore, population relevance, genotyping quality, and adherence to Hardy-Weinberg equilibrium were considered. Additionally, these variants have been investigated in the context of other diseases; their potential impact on CKD has not been thoroughly examined.

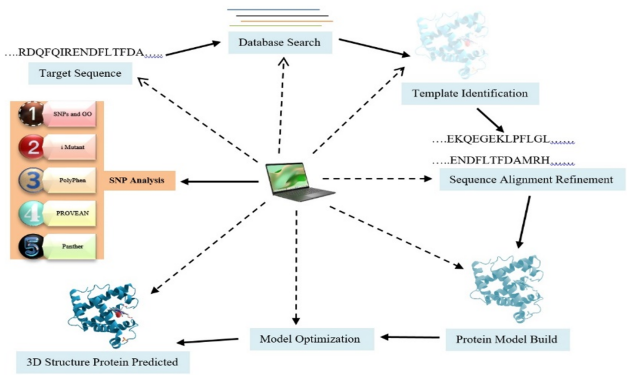

Figure 1. Diagram represents the overall processing of protein modeling and homology.

RESULTS

A. 3D Construction of Homo Sapiens XRCC1 and XPD Proteins

The amino acid sequences of the XRCC1 and XPD proteins (633 and 760 residues, respectively) were obtained from the National Center for Biotechnology Information (NCBI) database to generate a three-dimensional model. These sequences were subsequently submitted to the SWISS-MODEL server to predict the corresponding protein structures. The top-ranked 3D models were generated based on hundreds of template alignments and structural templates identified by LOMETS, a meta-server that searches the Protein Data Bank (PDB) library.

B. Construction of a Mutant Model of XRCC1 and XPD

The predicted models of XRCC1 and XPD obtained from the Swiss-Model server (model 1) were submitted to the Pyre2 server and YASARA software to generate mutant models of the wild-type proteins. Based on information from dbSNP/NCBI, specific amino acid substitutions were introduced: glutamine was replaced by arginine at position 399 (rs25487 T/C, Gln399Arg, missense variant Q [CAG] → R [CGG]); arginine was substituted with tryptophan at position 194 (rs1799782 G/A, Arg194Trp, missense variant R [CGG] → W [TGG]); lysine was replaced by glutamine at position 751 (rs13181 T/G, Lys751Gln, missense variant K [AAG] → Q [CAG]); and aspartic acid was substituted with asparagine at position 312 (rs1799793 C/T, Asp312Asn, missense variant D [GAC] → N [AAC]). The resulting 3D models of XRCC1 and XPD, depicting both the wild-type residues and the introduced substitutions, are shown in Figure 2.

C. Computational analysis of the effect of SNPs (rs25487 T/C) and (rs1799782 G/A) on XRCC1 protein and (rs13181 T/G) and (rs1799793 C/T) on XPD protein

Several key approaches across multiple subdisciplines were used to clarify the toxicological and severity-related effects [25]. They are not confined to a single discipline but can be applied across multiple fields involved in simulating xenobiotic metabolism [26, 27]. In omics sciences, in silico modeling plays a central role by providing precise computational simulations and analyses essential for interpreting complex biological systems [28]. XRCC1 and XPD are the proteins encoded by the XRCC1 and XPD genes. XRCC1 and ERCC2/XPD proteins participate in base excision repair and the pathway for repairing single-strand breaks [29, 30]. The computational servers, tools, and platforms employed enabled analysis of the impact of studied SNPs within the XRCC1 and XPD genes on protein function, structure, stability, and their association with disease.

D. Protein stability

The protein stability following amino acid substitution was assessed using the i-mutant server (http://gpcr2.biocomp.unibo.it/cgi/predictors/I-Mutant3.0/I-Mutant3.0.cgi) to evaluate the effect of substitution on the stability of the Homo sapiens XRCC1 and XPD proteins.

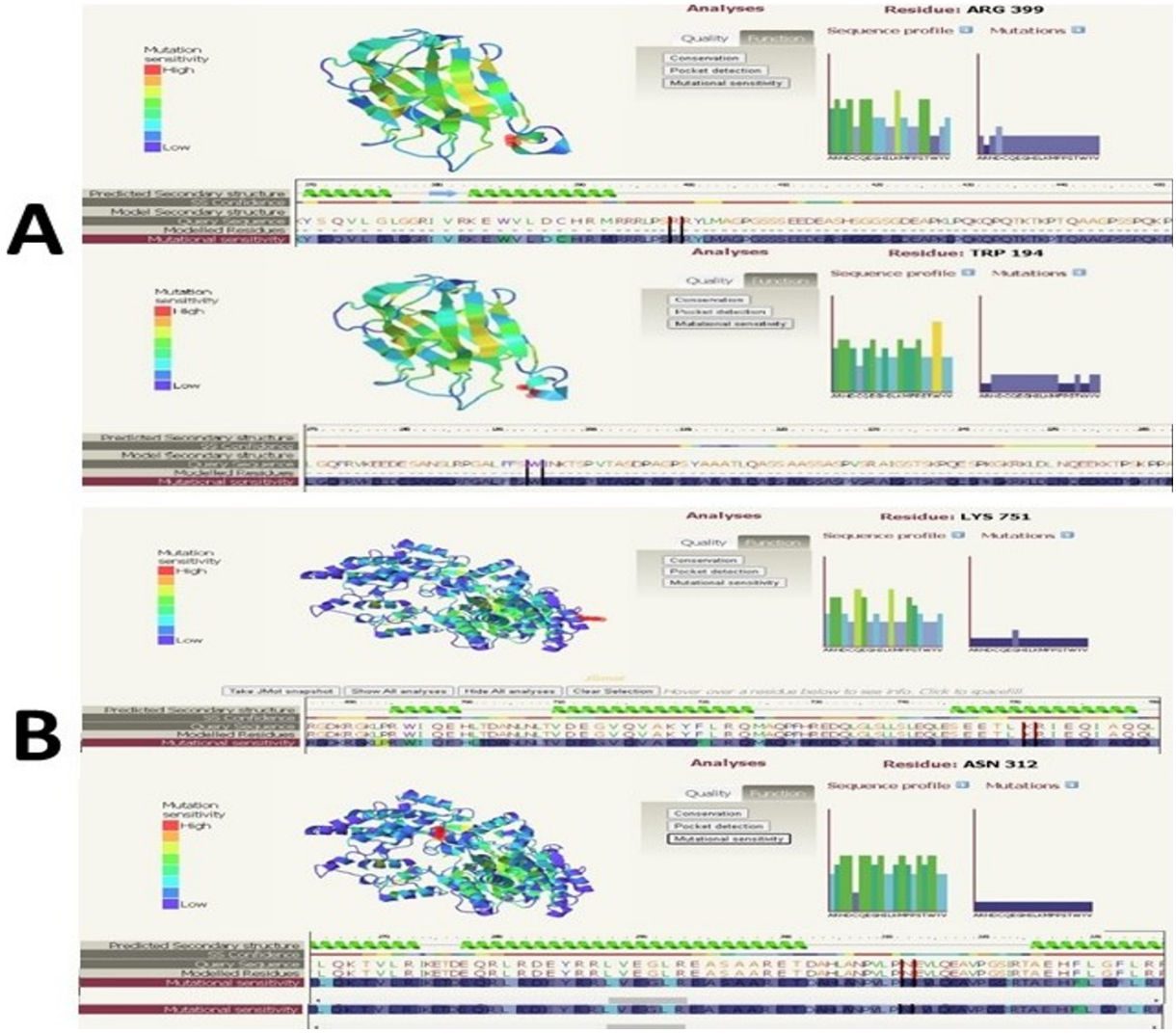

Figure 2. A: The predicted protein model of XRCC1 with polymorphism and mutation sensitivity of rs25487 (Gln399Arg) and rs1799782 (Arg194Trp) according to Pyre2. The red color in the 3D structure represents the mutation sensitivity according to scale and amino acid substitution. B: The predicted protein model of XPD with polymorphism and mutation sensitivity of rs13181 (Lys751Gln) and rs1799793 (ASP312ASN) according to Pyre2. The red color in the 3D structure represents the mutation sensitivity according to scale and amino acid substitution.

E. Analyzing SNPs structural and functional implications

Polyphen-2 was applied to analyze the structural and functional implications of the (rs25487 T/C), (rs1799782 G/A), (rs13181 T/G), and (rs1799793 C/T) variants. The assessment of the potential consequences of substituting an amino acid in the original protein structure, alongside evaluating the protein's function through multiple sequence alignment. The output categorizes of the impact as "probably damaging," "possibly damaging," or "possibly benign," were evaluated based on a score range of 0 to 1, as depicted in Figure 3.

F. SNPs biological impact

The investigated SNPs (rs25487 T/C and rs1799782 G/A) of the XRCC1 gene and (rs13181 T/G and rs1799793 C/T) of the XPD gene were confirmed to be harmful by utilizing the PROVEAN platform to assess their biological impact by distinguishing between neutral and harmful amino acids, based on a prediction threshold score of -2.5 (default). Variants scoring $\leq$ -2.5 were classified as harmful, while those scoring >-2.5 are considered neutral, as explained in Table 1.

G. Proteins categorization

The PANTHER Classification System was developed to categorize proteins (and their corresponding genes) for streamlined high-throughput analysis. It depends on a thorough, annotated "library" of gene family phylogenetic trees, as noted in Table 2.

Position-Specific Evolutionary Preservation (PSEP) measures the amount of time (measured in millions of years) that a contemporary protein's conserved position dates to its reconstructed direct predecessors. A stance is more likely to be harmful the longer it has been held. Based on results from the HumVar benchmark, this is converted into a probabil-

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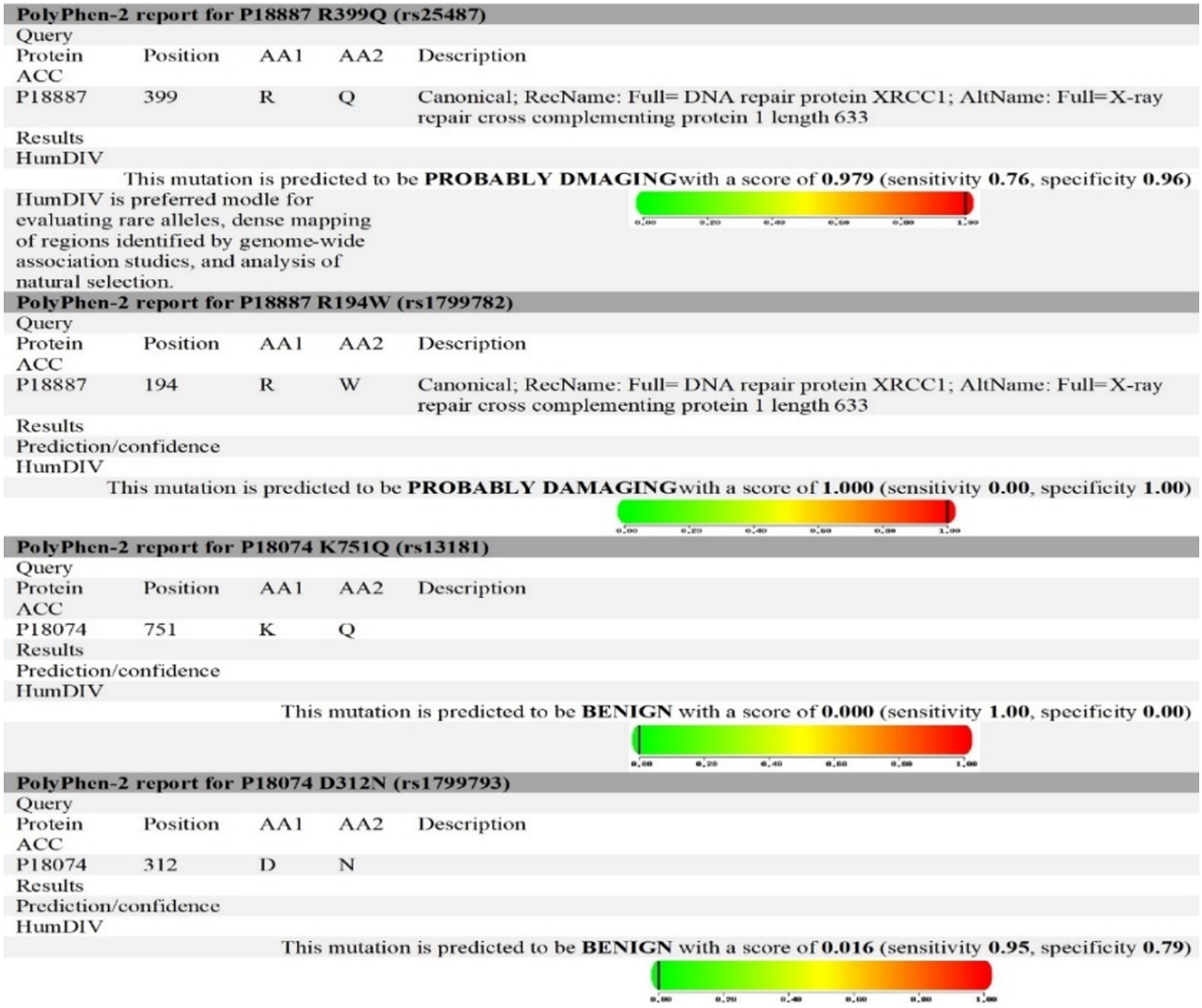

Figure 3. Represent Polyphen-2 output result and the benign and deleterious effect of the substitution with sensitivity 0.76%, specificity 0.96%, with 0.979 P-value and sensitivity 0.00%, specificity 1.00%, with 1.00 P-value for (rs25487 T/C) and (rs1799782 G/A) polymorphisms respectively, while the sensitivity 1.00%, specificity 0.00%, and sensitivity 0.95%, specificity 0.79%, with P-values of 0.001 and 0.016 value for (rs13181 T/G) and (rs1799793 C/T) polymorphism respectively.

ity of detrimental impact (Pdel). Pdel is then divided into three qualitative predictions: "possibly damaging" (for time between 450 and 200 million years, corresponding to a false positive rate of about 0.4), "probably damaging" (for time > 450 million years, associated with a false positive rate of approximately 0.2 as validated on HumVar), and "probably benign" (for time less than 200 million years).

H. The anticipated mutations

To anticipate mutations in XRCC1 and XPD genes associated with human diseases, particularly single-point mutations involving specific codons, and to track disease progression, the SNPs & Go server (https://snps-and-go.biocomp.unibo.it/snps-and-go/) was employed. A mutation was deemed significantly impactful for disease when it scored >0.05, as shown in the accompanying Table 2.

I. Protein-protein interaction

The physical connections that allow proteins to carry out coordinated biological processes including signaling, gene regulation, and metabolism are known as protein–protein interactions. Clarifying cellular networks and illness processes requires an understanding of these connections. One such tool that uses integrated computational evidence from several data sources to anticipate such connections is the STRING database.

The interaction of XRCC1 and XPD with other suggested proteins were applied based on the STING database, as shown in Figure 4. Evidence shows that different colors denote various types of evidence supporting these anticipated functional links. The network consists of 11 nodes out of 11 expected and 53 edges, and 11 nodes out of 12 expected and 52 edges, respectively, and an average node degree of 9.64 and 9.45, respectively and average local clustering coefficient of 0.968

Table 1. PROVEAN server output result of SNPs (rs25487 T/C, rs1799782 G/A) of the XRCC1 protein and (rs13181 T/G and rs1799793 C/T) of the XPD protein.

VARIATION		PROTEIN SEQUENCE CHANGE				PROTEIN PRODICTION				SIFT PRODICTION			
Row No.	Input	Protein ID.	Position	Residue_ref	Residue_alt	Score	Prediction (cutoff=2.5)	#Seq	#Cluster	Score	Prediction (cutoff=0.05)	Median_info	#Seq
1	NP_006288.2 399 Q R	NP_006288.2	399	Q	R	2.10	Neutral	77	30	1.000	Tolerated	2.86	51
1	NP_006288.2 194 R W	NP_006288.2	194	R	W	-4.42	Deleterious	77	30	0.001	Damaging	2.91	52
1	P18074 751 K Q	P18074	751	K	Q	-0.94	Neutral	158	30	0.582	Tolerated	2.90	151
1	P18074 312 D N	P18074	312	D	N	2.80	Deleterious	158	30	0.174	Tolerated	2.83	267

Table 2. The results of SNPs (rs25487 T/C) and (rs1799782 G/A) of the XRCC1 gene, and SNPs (rs13181 T/G) and (rs1799793 C/T) of the XPD gene, based on the i-mutant, Panther, and SNPs&Go platforms.

XRCC1	I-mutant Predictor of Protein Stability Changes upon Mutations					
Position	WT	NEW	Stability	RI	pH	T
399	Q	R	Decrease	1	7	25
194	R	W	Decrease	7	7	25
XPD	I-mutant Predictor of Protein Stability Changes upon Mutations					
Position	WT	NEW	Stability	RI	pH	T
751	K	Q	Increase	3	7	25
312	D	N	Decrease	2	7	25

PANTHER EVALUATION ANALYSIS OF CODING SNPS							
PANTHER HMM: DNA-REPAIR PROTEIN XRCC1 (PTHR 11370)				PANTHER HMM: DNA-REPAIR DEAD HELICASE RAD3/XPD SUBFAMILY MEMBER (PTHR 11472)			
Substitution	Preservation Time	Message	Pdel	Substitution	Preservation Time	Message	Pdel
R399Q	176	Probably Benign	0.27	K751Q	6	Probably Benign	0.02
R194W	750	Probably Damage	0.74	D312N	1237	Probably Damage	0.85
XRCC1	(SNPs&Go) SEQ File: P18887						
Position	WT	NEW	Effect	RI			
399	Q	R	Neutral	8			
194	R	W	Neutral	2			
XPD	(SNPs&Go) SEQ File: P18074						
Position	WT	NEW	Effect	RI			
751	K	Q	Neutral	3			
312	D	N	Disease	2			

and 0.953, respectively. The color of the lines indicates the type of evidence for the interaction, while in the "Confidence view," the thickness of the lines reflects the strength of the support for the interaction data. The blue and pink lines are well-known interactions, and the remaining are predicted.

DISCUSSION

The human XRCC1 and XPD proteins' three-dimensional structural models were effectively created in this work to enable an in-silico assessment of functionally significant SNPs. The SWISS-MODEL server, which combines multiple template alignments and structural predictions generated by the LOMETS meta-server, was used to model the protein sequences that were obtained from the NCBI database. Downstream mutational and functional studies were made possible by the structurally reliable representations of XRCC1 and XPD that were obtained from the top-ranked models selected based on template quality and alignment confidence. These models provide an essential foundation for comprehending the potential effects of amino acid changes on protein structure and biological function.

Later, disease-associated missense mutations found in the dbSNP database were used to create mutant models of XRCC1 and XPD [25, 26]. We therefore used Pyre2 and the YASARA software to model their structural consequences with respect to the XRCC1 variants Gln399Arg and Arg194Trp as well as the XPD variants Lys751Gln and Asp312Asn. SNPs were chosen based on known associations

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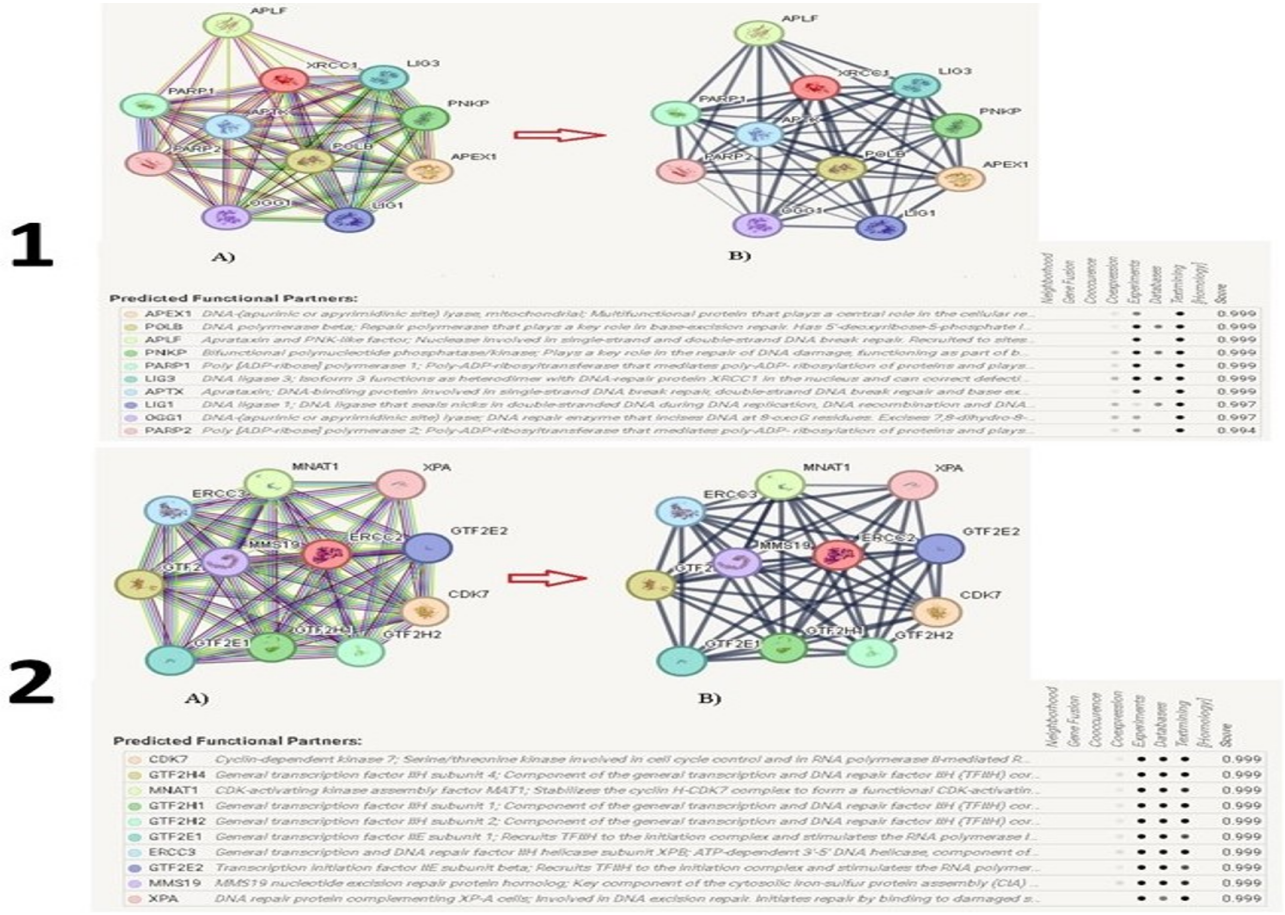

Figure 4. 1: The typical depiction of protein-protein interactions in the STRING database shows that XRCC1 interacts with ten proteins. A: Form indicated "Evidence view," B: Form indicated "Confidence view. 2: The typical depiction of protein-protein interactions in the STRING database shows that XPD interacts with ten proteins. A: Form indicated "Evidence view," B: Form indicated "Confidence view.

with cancer susceptibility and DNA repair efficiency [27]. As shown in Figure 3, structural comparisons of wild-type and mutant residues show localized conformational changes, indicating that these substitutions may disrupt pivotal functional domains or interaction surfaces. In silico analyses were carried out to assess the functional, structural, and pathological effects of the selected SNPs. Structural abnormalities that affect XRCC1 [base excision repair (BER)] and XPD [nucleotide excision repair (NER)] may destabilize genomic integrity [28]. A combined computational approach, considering several attributes including stability, evolutionary conservation and disease association was used to reflect the increasing use of these methods in toxicogenomic and precision medicine for prioritizing clinically relevant variants [29].

i-Mutant analysis suggested that the amino acid substitutions evaluated in this study were deleterious to XRCC1 and XPD thermodynamic stability. This loss of stability indicates an increased tendency of the protein to misfold or degrade, with harmful consequences for DNA repair function. Such structural effects of these variants could be detrimental and relevant for disease susceptibility, as suggested by such observations.

PolyPhen-2 analysis further classified variants as probably damaging or possibly damaging based on the physicochemical differences between wild-type and mutant residues, structural context, and sequence conservation. Similarly, PROVEAN predicted all the SNPs to be functionally deleterious when a predefined cutoff for detrimental effect was applied. This contingency held across diverse computational approaches, underscoring the robustness of these results.

Conservation analysis utilizing Position Specific Evolutionary Preservation (PSEP) and the PANTHER Classification System, reveals that multiple sites containing mutations are evolutionarily conserved for hundreds of millions of years. Alterations at these conserved positions are predicted to be functionally disruptive and, furthermore, validate their pathogenicity. Moreover, the SNPs and GO server analyses indicated that analyzed variants surpass pathogenicity thresholds and strongly affirmed their meaning as biomarkers for disorders in which DNA repair is impaired.

Such extensive interactions of XRCC1 and XPD with other DNA repair and genome maintenance proteins were observed by performing protein–protein interaction network analysis via STRING database. Such networks form with high-degree nodes, dense connectivity and a large clustering coefficient due to healthy functional integration mediated by experimental interactions.

The overall evidence indicated that both XRCC1 and XPD

polymorphisms were associated with negative outcomes, although there was some variability in results depending on the algorithms/assumptions used for individual prediction tools. Divergences between sequence-, structure- and stability-based approaches highlight the value of integrative consensus analyses. These variants may have clinical implications, including reduced repair efficiency and increased susceptibility to chronic diseases. Damage-repair deficiency exacerbates oxidative stress, promotes inflammation and adds to genomic instability at the cellular level. This may cause renal cellular damage and expedite the advancement of kidney disease (e.g., CKD) [30]. While further in silico predictions will require the eventual validation by experimental data, these findings lay the mechanistic groundwork linking XRCC1 and XPD variants to cellular function deficits that contribute to disease susceptibility.

This study has several limitations. First, it relies solely on in silico analyses without experimental validation. Second, only a limited number of SNPs were examined, which may not fully capture the genetic variability of the XRCC1 and ERCC2/XPD genes. Additionally, the use of predicted protein structures may not accurately reflect the dynamic behavior of proteins in biological systems.

CONCLUSION

XRCC1 variants rs25487 and rs1799782 had predicted in vitro protein stability, whereas their predicted protein stability differed, as indicated by the i-Mutant server for polymorphisms of XPD, rs1799793 reduced status of polymorphisms decreased, while the variant rs13181 was slightly increased. In contrast, functional predictions based on PolyPhen-2 suggested that XRCC1 variants were likely to be damaging, whereas those for XPD were predominantly predicted to be benign. Analysis using PROVEAN suggested that rs25487 and rs13181 are likely neutral, while the changes involved by rs1799782 and rs1799793 would lead to deleterious amino acid polymorphism. Remarkably, the SNPs and GO platform showed that rs1799793 was significantly associated with disease susceptibility, indicating its pathogenic significance. All our results point to the likelihood that variation in XRCC1 and XPD may affect protein structural stability and function, especially when substitutions occur in conserved regions, increasing the risk of illness by impairing DNA repair processes.

ETHICAL DECLARATIONS

Acknowledgments

None.

Ethics Approval and Consent to Participate

Ethical approval for the study was obtained from the MECC and the Najaf Health Directorate. The approval was granted in accordance with institutional regulations under form number 9695, dated March 13, 2025. All patient data were anonymized and handled in accordance with ethical standards to ensure confidentiality and privacy. No patient consent was needed as the study involved data collected from patients' reports.

Consent for Publication

Not applicable as there is no need for participants' photos or personal information.

Availability of Data and Material

The datasets generated and analyzed in the current study are available from the corresponding author upon reasonable request, subject to ethical approval and data sharing agreements.

Competing Interests

The authors declare that there is no conflict of interest.

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Use of Artificial Intelligence

The authors would like to recognize the use of the Grammarly artificial intelligence tool to enhance the writing quality of this manuscript.

Authors' Contributions

Conceptualization: Al-Koofee DAF and Hussain JM. Data curation: Abo-Ghneim FDF. Statistical analysis: Al-Koofee DAF. Investigation: Abo-Ghneim FDF, Hussain JM, and Al-Koofee DAF. Methodology: Al-Koofee DAF and Hussain JM. Project administration: Hussain JM, Al-Koofee DAF. Writing – original draft: Abo-Ghneim FDF and Al-Koofee DAF. Writing -review and editing: Abo-Ghneim FDF, Al-Koofee DAF, and Hussain JM. All authors read and approved the final version of the manuscript.

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