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Cancer and the influence of DNA repair gene XRCC1 Polymorphism: A Review

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Abstract

The XRCC1 (X-ray cross complement protein 1) polymorphism has been demonstrated to act as a scaffold for DNA repair that can be plays a role in the progression of a variety of cancers such as breast, lung, head and neck, cervical and others. This polymorphism participates in multiple repair pathways and facilitates base excision along with single strand break repair. They have many functional polymorphisms that may result directly from damage to deoxyribose or indirectly through common intermediates of base expression repair for the treatment of serious diseases such as cancer. It functions as an essential co-transporter for a number of other repair proteins, such as DNA ligase 3α (LIG3), aprataxin, and PNKP-like factor (APLF). When XRCC1 binds to highly specific areas, it helps coordinate specific repair process by recruiting additional enzyme. This allow XRCC1 to managewide range of issues that arise during repair or in other repair pathways with which it interfaces. Numerous studies with varying conclusions have examined the association between the prognosis of HNSCC and the XRCC1 Arg 399Gln genetic polymorphism. Therefore, the present study aims to review cancer diseases and the influence of XRCC1 polymorphism as well as the repair mechanisms within which these interactions function. Study mainly based on the published articles; which is explored by Scopus, web of science, PubMed international database and others. Numerous genetic models declared that there was no significant association with cancer risk between the XRCC1 Arg 399Gln polymorphism.

Key words : XRCC1 polymorphism, Base excision repair, DNA repair, and Cancer.

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Cancer, a malignant disease characterized by uncontrolled abnormal growth of cells that begins in an organ or tissue and spreads beyond its borders to invade nearby parts of the body and spread to other organs. Many identified types of cancer have been linked to organ systems which can be also developed through PAHs (Polycyclic aromatic hydrocarbons) related group of chemicals present in environments and the variety of products (Figure 1). Globally, it is one of the leading causes of death. The cancer disorder mainly caused by two important appearances *i.e.*, somatic cell mutation and abnormal cell mutation, which effectively affect the human/ animal tissue or organ system. These altered neoplastic cells have the capacity to spread and infiltrate different bodily areas. About 90-95% of cancer are caused by genetic mutations while only 5% are inherited[49,92].

In India, cancer is gradually acting as a serious health threat that affects people from all socio-economic backgrounds and geographical regions. It is a matter of concern that every year the number of cancer patients registered across the country is continuously increasing. Numerous scientists have recorded that, since 1981, seven thousand seven hundred fifty-seven sources of data from hospitals, laboratories, and other agencies have been used by the NCRP (National Cancer Registry Programme), which is housed under the ICMR-NCDIR (Indian Council of Medical Research-National Centre for Disease Informatics and Research) Bengaluru, to systematically collect data on cancer in India. It offers trustworthy information about newly discovered cases of cancer, historical trends, shifting patterns and their distribution, cancer treatment methods, and cancer outcomes and survival rates. These inputs monitor effects, guide action, and promote pertinent research[13,28].

Cancer encumbrance in India :

India is expected to have 1,496,972 cases of cancer in 2023, up from 1,461,427 in 2022, with only

9:1 people expected to be diagnosed with cancer at some point in their lives. Notably, the most prevalent cancers among Indian women were breast cancer and among males, lung cancer. Among children ages 0 to 14,

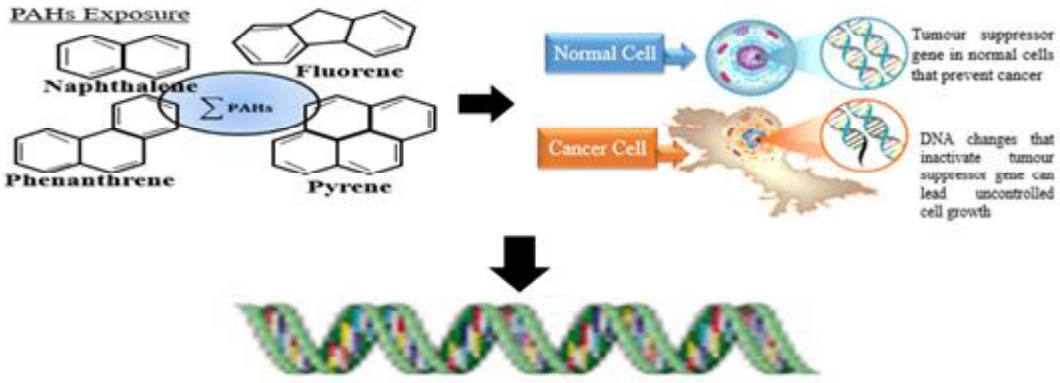

Figure 1. Chemical Structure of few carcinogens responsible for XRCC1 polymorphism.

lymphoid leukaemia is the most frequent type of paediatric cancer, affecting 24.2% of girls and 29.2% of boys. In comparison to 2020, there will likely be a 12.8% rise in cancer incidence by 2025 [79]. According to projections, India's cancer incidence is projected to increase from 26.7 million in 2021 to 29.8 million in 2025, with the north and northeast experiencing the greatest burden. Cardiovascular disease (63.3%) is the leading cause of death among non-communicable diseases, followed by cancer (18.1%). A decrease in premature death is indicated by the increase in disability-adjusted life years for cancer. Using digital advances, efforts should concentrate on maintaining and expanding Non Communicable Disease (NCD) screening, education, health promotion, and tobacco control at the community level. The incidence of cancer is on the rise in India due to a number of variables, including underlying genetic predispositions, environmental factors, and changes in lifestyle. Alcohol and tobacco use were found to be prevalent in 32.8% of respondents to the National NCD Monitoring Survey (NNMS), which was conducted in 2017-2018. Among adults, the mean salt intake was 8 g per day, more than one-third (41.3%) were physically sedentary, and nearly all (98.4%) consumed fewer than five servings of fruits and/or vegetables daily. India's growing cancer rate poses a serious threat to public health[61,79].

Numerous techniques/strategies are universally employed in the assessment and restoration of DNA damage. After exposure to a range of stressors, including ultraviolet (UV) radiation, DNA alkylators, specific environmental carcinogens, oxidative stress, and chemotherapy drugs. Each of these harmful agents results in DNA lesions and base modifications that encourage a break in the DNA helix. Because double-strand breaks (DSBs) damage both strands of DNA and encourage the loss of genetic information, they are fatal to cells. Damage to DNA, which is common in eukaryotic cells, can lead to genomic instability and facilitate the onset of several diseases, including cancer. Cellular reactions are triggered after DNA damage, enabling the cell to repair the damage or process. Common polymorphisms in DNA repair genes can impact an individual's capacity to repair damaged DNA, which can lead to genetic instability and carcinogenesis [8,11,19,46,74]. In mammalian cells, the protein XRCC1 is involved in the repair of Single Strands Breaks (SSBs) through interactions with several enzymatic components of repair events. Therefore, present study aims to review cancer diseases and the influence of XRCC1 polymorphism.

XRCC1: Structural perspective :

X-ray cross complementing group 1 protein (XRCC1) was the first mammalian gene shown to aid in shielding the cell from ionising radiation's effects. It was later demonstrated to offer defence against many forms of stress, such as UV-induced damage and alkylation. Although the protein does not appear to have intrinsic enzymatic activity, it does interact with a number of repair enzymes that are part of the single-strand break repair (SSBR) pathway. Scientifically, population-based evidence confirms the following associations: (a) reduced risk of various type of cancer due to the XRCC1 R194W variations, (b) increased risk of breast cancer due to the BRCA2 N372H variant, and (c) risk of various types of cancer due to the 8-oxoguanine DNA glycosylase (OGG1) S326C variant. Molecular

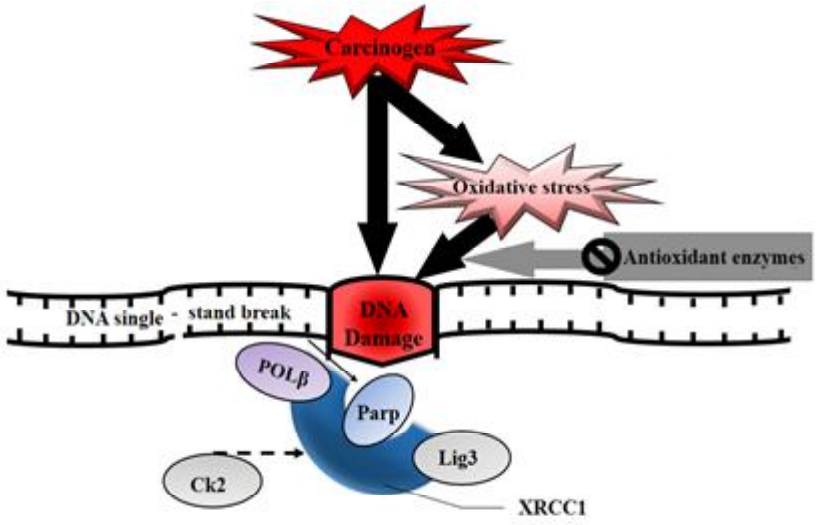

Figure-2. XRCC1: Structural perspective - reacting to environmental carcinogen-induced DNA single-strand breaks with implicated protein partners.

systems designed to repair damaged DNA are being increasingly appreciated based on suggestive results for polymorphisms in other genes. The process by which base damage is treated is known as "base excision repair", which entails glycosylase removal, processing by proliferating cell nuclear antigen/Pol β-dependent long-patch repair or XRCC1-assisted Pol β-dependent short-patch repair. The SSB are repaired by activation of poly (ADP-ribose) polymerase (PARPs), and XRCC1; then after it followed by requirement of more proteins that involved in the repair process[30]. [Figure - 2]

The DNA repair gene "XRCC1" has been thoroughly investigated in several cell lines (by in-vitro or in-vivo experimentations) because to its involvement in multiple repair pathways and its protein product. It is the first human identified gene composed of 17 exons and spans a genomic distance of 32 kb, as well positioned on chromosome 19q32-133. Similarly, the XRCC1 maps of Mouse/animal's also has a parallel position located on 7th chromosome and spans with 26kb. Three interaction domains as well as a nuclear localization signal and a phosphorylation site for Casein Kinase (CK2) have been identified in XRCC1, but it is not associated with any known enzymatic activity[1,64,81]. [Figure - 3]

XRCC1: Protein structure description :

XRCC1, is a 70KDa protein required to repair of BER and single strand breaks (SSBs). Despite the protein's absence of inherent enzymatic activity, these processes nevertheless take place. According to theory, XRCC1 functions as a scaffold protein that makes it easier for DNA repair enzymes to recruit and serves as a loading platform for the repair procedure. XRCC1 interacts with a series of DNA repair enzymes, each of which

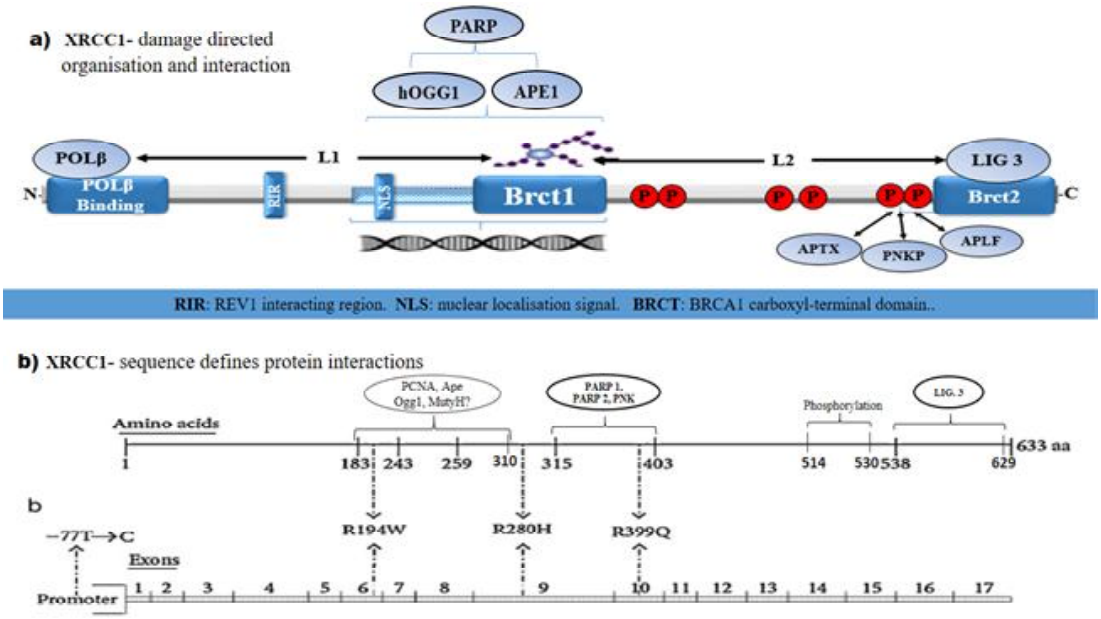

Figure-3. Significant polymorphic areas and protein domains that are known to be associated with other elements of base excision repair are found in the human XRCC1 gene and protein structure. The obtained sequence defines protein interactions

has a unique binding specificity for one of its functional domains [Figure - 3, a]; where (a) The N-terminus region is bound by DNA polymerase ? (POL?); (b) the middle region, which contains the nuclear localization signal and breast cancer susceptibility protein-1 homology C-terminus (BRCT) I domain, bound by AP endonuclease-1 (APE1) and human DNA glycosylase, (c) BRCT I domain bound to poly (ADP-ribose) polymerase (PARP), and (d) the C-terminus is bound to the BRCT II domain DNA ligase III (LIG3). The XRCC1 structure has the identical BRCT I and II domains as the Breast Cancer Gene 1 (BRCA1), which have generated a great deal of attention in the field of cancer research[15,16,18,37].

SSB repair is carried out according to the type of DNA damage. This time these damaged bases were eliminated. This procedure produces indirect SSB by mean of base excision repair (BER), which is initiated by eliminating a damaged nucleotide. This includes processes commonly known as short patch repairs, *i.e.*, a small number of bases produced [Figure - 3, b]. The term "short patch repair" is frequently used to describe it because it only requires a small number of removed bases. A single or multiple nucleotides can be inserted at the gap location by Pol β, which can carry out both short- and long-term patch repairs. After the initial incision, XRCC1, a secondary binding element, is drawn to the patch region where it may stabilise intermediate DNA structures like basic sites and draw in more repair enzymes[14,96]. It forms complexes with

LIG3 and Pol β, which helps LIG3's ligase activity to close the repaired break and allow the insertion of new nucleotides. LIG3 may use its inherent nick-sensing ability to attract the LIG3-XRCC1 complex to the repair site. The precise nature of the protein complex between XRCC1 and LIG3 or whether the two bind in a repair capacity is unknown[37,69,75,87]. As a direct consequence of DNA damage from oxidation or alkylation, SSBs can also happen without the need for DNA repair. When PARP detects these SMBs, the XRCC1-LIG3 complex is drawn to the area (Figure - 3, b). This entails a lengthy patch repair procedure that works similarly to a short patch repair procedure. Additionally, polynucleotide kinase (PNK), an enzyme whose capacity to distinguish between SSB is boosted in the presence of XRCC1, can aid in sealing of the damaged termini. Hence, although lacking enzymatic activity, XRCC1 can interact with other enzymes that act on SSB to participate in a range of distinct DNA repair mechanisms[75].

Numerous *in vitro* models have confirmed XRCC1's involvement in SSB repair. It is known that some Chinese hamster ovary (CHO) cells (EM7, EM9, and EMC11) have high amounts of sister chromatid exchange (SCE) and SSB, and that they lack the XRCC1 protein. These cell lines exhibit hypersensitivity to radiation and alkylating chemicals. In example, the EM9 cell line is 1.8 times more susceptible to ionising radiation and 10 times more hypersensitive to death when exposed to ethyl methane sulfonate than its mother cell line. EM9 cells that have had the human XRCC1 gene transfected into them develop resistance against both spontaneous and genotoxicant-induced SSBs[17,29,58]. The XRCC1 null mice have provided whole animal evidence supporting the significance of XRCC1. The development of the null line is stopped on embryonic day 6.5, resulting in morphologic defects and mortality, and these mice do not survive the foetal environment-not even in the absence of exposure to chemicals that damage DNA. XRCC1 null animals also have much lower levels of other DNA repair proteins, such as LIG3, which may suggest that XRCC1 is involved in promoting LIG3 expression or activity. Nevertheless, it is interesting to observe that mice expressing as little as 10% of XRCC1 did not display aberrant post-natal development or embryogenesis, and their sensitivity to MMS was only slightly increased. Although XRCC1 is expressed in many different tissues, it is not consistent. In primates, the testis is where XRCC1 is most abundantly expressed, followed by the ovaries and the cardiac tissue. The distribution of XRCC1 expression in rodent tissue is similar. The concept that DNA repair is essential for protecting the template during germ-line meiosis is supported by the robust expression of XRCC1 in gonadal tissues[58,96].

Determination of XRCC1 Polymorphism and Cancer :

XRCC1 (X-ray repair cross complementing 1) gene belongs to the family of complement genes, which comprises over 20 identified genes. These genes are involved in DNA repair through various mechanisms; for example, XRCC2 and XRCC3 are believed to perform via double-strand homologous recombination, which is the process of genetic material crossing over between paired chromosomes, while XRCC4-XRCC7 are thought to perform via double-strand non-homologous end joining,

which is the process of exchanging genetic material that differs from the damaged template. Instead, XRCC1 is engaged in the BER-based SSB repair, as mentioned in the preceding section[34,72,76].

The polymorphic variations of the XRCC1 protein, R194W (rs1799782), R280H (rs25489), and R399Q (rs25487), are widely investigated in relation to the development of cancer. The XRCC1 protein plays a pivotal role in base excision repair. In the depth reports on cancer epidemiology, panel of 90 human lymphoid cell lines was used to identify 27 different XRCC1 gene variations related to its functional component. Among these, there are eight non-synonymous SNPs, twelve insertions/ deletions, four synonymous SNPs, and three 5' UTRs. Nevertheless, research on two polymorphisms in populations has been done[50,89]. The two most widely utilised varieties, R399Q and R194W, have not been the subject of more in-depth research. This makes it possible to examine comparable group sizes and data sets more thoroughly. Due to its small population size, the third polymorphism, R280H, has also been studied, albeit less frequently[10,31,91]. [Figure - 4]

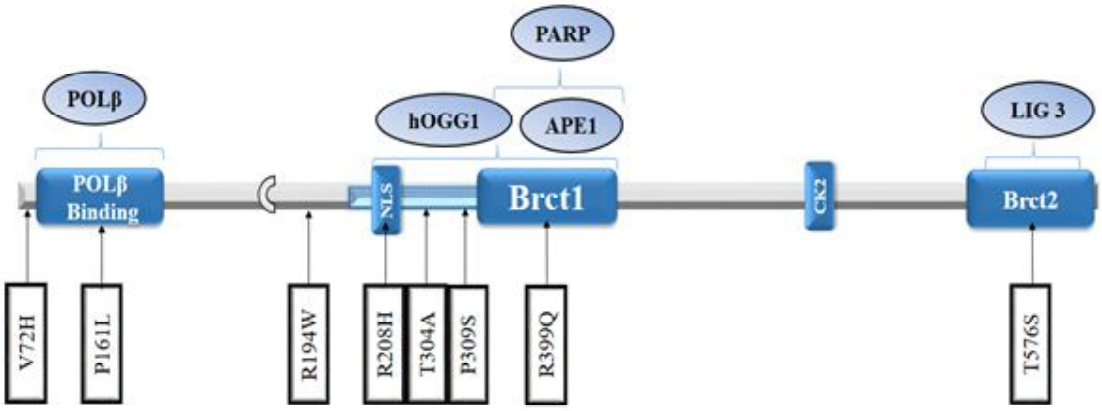

Figure-4. Human XRCC1 domains and positions of the eight known non-synonymous single-nucleotide polymorphisms (SNPs) that alter an amino acid residue.

R194W :

Recent research indicates that the R194W SNP is crucial in lowering the chance of developing cancer. Supported by multiple published studies, a meta-analysis of case-control and cohort studies on Chinese populations comprising 18 studies with 3915 cases of gastric cancer (GC) and 6759 controls revealed that the homozygous mutant genotype (W /w) of XRCC1 R194W was linked to an increased risk of Gastric Cancer (GC)[62]. The Russian study involving over 2000 cases declares that those in the top quartile of pack-years of smoking had a lower risk of lung cancer while taking R194W [56]. These findings are unexpected because it was generally believed that changes in amino acids consumption would negatively impact function and raise the risk of cancer.

The research-oriented statics for R194W are reasonably consistent across a wide range of research, indicating the possibility of a valid inverse relationship. The second factor to take into account is the lack of a direct relationship and simply a relationship to another causal gene or other relevant polymorphism that is a component of the haplotype. Studies on cellular function will help solve this problem. Third, protein binding can be improved by modifying the amino acid composition. A number of interacting protein partners, including Proliferating Cell Nuclear Antigen (PCNA), apurinic/apyrimidinic endonuclease 1 (APE1), and various glycosylases, including 8-oxoguanine DNA glycosylase (Ogg1) and MutyH, have putative binding domains that include the 194 locations[32]. Tryptophan signalling changes from positively charged arginine to hydrophobic tryptophan, which may impair binding and DNA repair effectiveness as this region is rich in proline, serine, arginine, and lysine residues. It's intriguing that in silico simulations suggest that the presence of the W allele may have deleterious effects and result in an intolerant protein. It's unclear whether this contradicting evidence signifies, but further functional research is required. Finally, it's possible that an overexpression of a different gene that speeds up DNA repair is brought on by the alteration in amino acid structure[82].

The XRCC1 null and variant alleles have been studied functionally *in vitro* using Chinese hamster ovary (CHO) cell lines. The comparatively simple isolation of mutants exhibiting phenotypic sensitivity to compounds that cause high amounts of single-strand breaks (SSB), like methyl methane-sulfonate (MMS), can be attributed to the hemizygosity of the XRCC1 gene in CHO cells. It was discovered that one mutant clone, known as EM9, carries a frameshift mutation that produces a shortened polypeptide that is missing two-thirds of the original sequence[44]. According to Takanami *et al*.[90], plasmid constructs were created that were transfected into EM9 CHO cells expressing R194W or R280H or XRCC1 wild-type. After exposure to MMS, survival of these cells was evaluated. The R194W-transfected cells had a higher survival rate comparable to that of transfected wild-type cells, whereas the EM9 cells had a poor survival rate. Thus, the functional investigation conducted in vitro does not conflict with the epidemiology research.

R280H :

Research on the R280H SNP has been less extensive than that of R194W and R399Q, due to the low frequency of the allele and the large sample size required to complete adequate power analyses. According to the performed research by Hu *et al*.[35]; a meta-analysis of eight case-control studies found that people with the arginine/arginine genotype had a significantly lower risk of cancer than people with the histidine allele. Conversely, those homozygous for the arginine gene and those in the top quartile of pack-year smokers were more likely to develop lung cancer than those with the histidine genotype. The results point to a possible relationship that might be impacted by environmental exposure, even though they are not sufficient to draw solid conclusions. In their investigation, some scientists showed that resistance was not restored when the R280H variant was transfected into a methyl methane sulfonate (MMS)-sensitive CHO cell line that was null for the XRCC1 gene product[50].

Methyl Methane Sulfonate (MMS) is

an alkylating agent that generates SSB in DNA, which needs to be repaired effectively by XRCC1. Previous studies suggest that the histidine allele may be detrimental to XRCC1 function. This study employing the comet test revealed that, in contrast to Chinese hamster ovary (CHO) cells with the arginine genotype, certain CHO cells with the histidine genotype exhibited a notable delay in SSB repair at 60 minutes. Additionally, they demonstrated that the histidine-transfected CHO cells treated with MMS had less NADPH, indicating a possible link between PARP1 activation and XRCC1 function[27].

R399Q :

The R399Q SNP has drawn the most attention from researchers of all the DNA repair gene variants, making it the most investigated XRCC1 polymorphism as well. Various scientist claimed that R399Q has revealed connotations that work in different ways for several types of cancer[55]. As an instance, the risk of non-melanoma skin, oesophageal, and bladder cancer decreased, but the risk of stomach and lung cancer increased. In their meta-analysis study, no evidence was found in a general link between genotype and cancer risk or cancer prevention[99]. However, the risk was significantly higher for Asian and African when categorized by ethnic background. Some earlier research reported no association between the R399Q variation with lung cancer incidence in a study of over 2000 cases and controls in Eastern Europe. Because of this, epidemiological findings do not provide any solid evidence that the XRCC1 R399Q SNP is directly associated with cancer. Moreover, recent studies have shown that the sensitivity of R399Q cells transfected with the R399Q gene to MMS, which did not differ from Q399R cells[5,78].

Furthermore, the comet test revealed no difference in the two isoforms' abilities to correct SSB brought on by MMS. R399Q cells' sensitivity to MMS did not change when Q399R cells were transfected with the R399Q gene. Additionally, the comet assay revealed no difference in the two isoforms' abilities to repair MMS-induced SSB. Generated evidence indicating that exposure of wholeblood cells from people with the R399Q genotype causes a substantial increase in chromosomal deletions using cytogenetic irradiation and UV light challenge experiments. It follows that chromosomal deletions are caused by inadequate DNA repair, which would promote genetic instability and raise the possibility of cancer-causing mutations[43].

XRCC1 polymorphism consequences and its function :

The relationship between the XRCC1 gene polymorphism and cancer risk has been evaluated in numerous studies. Myelodysplastic syndrome risk is linked to polymorphisms in XRCC1 (Arg280His). The clinical results of platinum-based chemotherapy may be considerably impacted by XRCC1 Arg399Gln and XPG His46His. The XRCC1 gene has genetic variants that are linked to an increased risk of colorectal cancer[101]. Some specific research declared that, more than 60 nucleotide polymorphisms (SNPs) have been identified with the most extensively investigated coding region SNPs being Arg399Gln on exon 10 (G to A; rs25487), Arg194Trp on exon 6 (C to T; rs1799782), and Arg280His on exon 9 (G to A; rs25489). The sites of these coding region

SNPs are noted within the functional domains stated. [Figure -3]

Mutations in the BRCT I domain of the BRCA1 tumour suppressor gene have been associated with decreased activity; however, the precise role of this domain within the XRCC1 protein remains unclear. While the prevalence of these mutations in the general population is covered in a later section, the discussion that follows concentrates on how the polymorphisms may affect XRCC1 function as previously mentioned. Many of the in-vitro models have been used to assess the impact of the XRCC1 genotype on a cell's capacity to repair DNA damage[15,43]. The most widely used system compares the ability of human lymphocytes challenged with a DNA-damaging agent to repair the damage among persons with various genotypes. This fundamental test technique can be modified by inflicting DNA damage on a surrogate cell line (such as HeLa cells), the nuclei of which are subsequently cultured with human lymphocyte extracts from people with XRCC1 polymorphism genotypes[15].

HeLa DNA damage can be repaired by XRCC1 and additional repair proteins found in the lymphocyte extract. Most of these systems' results are consistent with the idea that the XRCC1 genotype influences repair capacity[12,27]. The evidence is not totally consistent, and other studies indicate no effect, therefore the effects may be small. Evidences is summarised in Table-1. Although it was suggested that the polymorphism had a protective effect, the data lacked statistical significance. Due to the zero frequency of the homozygous variant in this small study sample, it was not possible to evaluate its impact. Wang *et al*.[98] assessed the impact of the Arg194Trp genotype on the ability to repair DNA in a more extensive population.

DNA repair experiments involve multiple damage factors [Table -1], some of which are more likely to implement BER than others and call for XRCC1. Bleomycin is one such example of a radiomimetic medication whose radical reactions cause oxidative DNA damage that is susceptible to base-excision repair (BER). Nucleotide excision repair (NER) is the mechanism used to repair the bulky DNA adducts caused by benzo (a) pyrene-diol-epoxide (BPDE) as opposed to BER, and XRCC1 is not known to play a role in NER. 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), a nitrosamine unique to tobacco, generates a range of large and less complex adducts that activate both NER and BER. It is probable that the additional therapies indicated in Table - 1 caused the kinds of ionising radiation, oxidative, or alkylation damage necessary to cause BER and call for XRCC1[15,20,71].

The impact of the Arg194Trp genotype on DNA repair capacity was assessed in three investigations using three distinct chemical treatments. Sister chromatid exchange (SCE), chromosomal breakage, or other markers of DNA damage were measured in each investigation using human cells. Abdel-Rahman *et al*.[2], and El-Zein, *et al*.,[26] assessed the impact of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) on lymphocytes extracted from forty-seven healthy subjects. Before being harvested, lymphocytes were subjected to NNK for three hours, twice washed, and then given a 40-hour incubation period. With

increasing NNK concentration, they observed an increase in mean SCE frequency; the wild-type response was larger than that of the heterozygous variation (Table - 1). Despite the fact that the results did not achieve statistical significance, this would suggest a protective effect of the polymorphism. It was not possible to evaluate the impact of the homozygous variant due to its zero frequency in this small study population.

In a broader cohort, Wang *et al*.,[98] assessed the impact of the Arg194Trp genotype on DNA repair capacity. The mean number of chromosomal breakages per cell was measured in lymphocytes isolated from 524 healthy persons after they were treated to either bleomycin or benzo (a) pyrene-diol-epoxide (BPDE). After being treated to bleomycin for five hours or BPDE for twenty-four hours, lymphocytes were exposed to colcemid for the final hour of exposure in order to stop the cell cycle during mitosis. Analysis was done comparing the wild-type to a combined group of homozygous plus heterozygous variations because of the low frequency of the homozygous variant (n = 3). Comparing the wild-type to the homozygous/heterozygous variation group, this investigation showed a considerable increase in the number of chromosomal breaks, which is in line with the findings reported byAl Mashhadani, *et al*.,[4] and Abdel-Rahman *et al*.,[2]. This small effect happened despite the fact that NER, not BER, is used in the repair of BPDE-induced DNA adducts. When comparing the mean number of chromatid breaks per cell caused by bleomycin for Arg194Trp variations with wild type, Tuimala *et al*.,[94] found no statistically significant differences. [Table-1]

Numerous DNA damage studies have been conducted to assess the impact of the Arg399Gln SNP. Abdel-Rahman, *et al*.,[2] examined the Arg194Trp SNP in human lymphocytes obtained from the previously reported sample of 47 healthy donors. In response to NNK, the combined heterozygote/ homozygote variant group's mean SCE score increased statistically significantly when compared to the wt. group [Table-1]. Therefore, the 399 variant seems to increase vulnerability for genotoxic effect, in contrast to the apparent protection provided by the Arg194Trp variant allele. The 524 people who were assessed for the Arg194Trp SNP previously mentioned were also assessed for Arg399Gln. After being exposed to bleomycin, the wild-type and Arg399Gln heterozygous variants showed similar frequencies of chromosome breakage in their lymphocytes; however, the homozygous variation showed a slight but significant increase (16% increase, P = 0.033). Since there was no SNP-associated change in chromosomal breakage in response to this mutagen, these results could not be repeated in the BPDE-exposed cells. This is not unexpected because BER cannot reverse DNA damage caused by BPDE. Tuimala *et al*.,[94] didn't find any impact of the Arg399Gln SNP on chromosomal breaks caused by bleomycin, even though this chemical causes damage that can be repaired by BER.

Moreover, the production of micronuclei-small DNA fragments with cytoplasmic bodies that indicate acentric chromosomal fragments-has been used as an indicator of the ability to repair chromosomal damage. The DNA repair capacity of lymphocytes obtained from 199 individuals exposed to bleomycin and genotyped for the codon 399 SNP was examined

Table-1: Influence of XRCC1 genotype on DNA repair.

SNP (N)	Endpoint	Study protocol	Results	References
Arg280His **Arg/Arg (n = 69)** **Arg/His & His/His (n = 11)**	Bleomycin-induced b/c	Lymphocytes exposed to bleomycin for 5 h without washout and b/c measured.	25% mean increase in b/c seen in combined variant group compared to wt (P = 0.002).	(J. Tuimala, et al., 2002; Ginsberg, et al., 2011).
Arg280His **Not a population study**	Hydrogen peroxide or methyl methanesulfonate-induced NADPH depletion.	Transfected EM9 cells carrying wt or variant allele incubated with genotoxic agent without washout.	Large depletion of NADPH in cells carrying 280 variant allele, with smaller effect of 399 variant allele.	(B.F. Pachkowski, et al., 2006; Ginsberg, et al., 2011).
Arg194Trp **Arg/Arg (n = 72)** **Arg/Trp(n = 8)**	Bleomycin-induced b/c	Lymphocytes exposed to bleomycin for 5 h without washout and b/c measured	No significant difference seen across genotypes	(J. Tuimala, et al., 2002; S. Z. Abdel-Rahman, et al., 2011).
Arg194Trp **Arg/Arg (n = 42)** **Arg/Trp (n = 5)**	NNK-induced SCEs	Lymphocytes exposed 3 h to NNK with washout and allowed to incubate for 40 h prior to harvest.	1.2–1.6-Fold increase in SCE in Arg/Arg when compared to heterozygote rate (P > 0.05).	(S.Z. Abdel-Rahman, et al., 2000; S. Z. Abdel-Rahman, et al., 2011).
Arg194Trp[a] **Arg/Arg (n = 461)** **Arg/Trp&Trp/Trp (n = 73)**	BPDE-induced chromosome. breaks/cell (b/c) Bleomycin-induced b/c	Lymphocytes exposed 24 h to BPDE without washout and b/c measured. Lymphocytes exposed 5 h to bleomycin without washout and b/c measured.	16% mean increase in b/c in Arg/Arg compared to variant group (P = 0.005). 14% mean increase in b/c in Arg/Arg compared to variant group (P = 0.054).	(Y. Wang, et al., 2003; Xiao, et al.2016).
Arg399Gln[b] **Arg/Arg (n = 19)** **Arg/Gln (n = 25)** **Gln/Gln (n = 3)**	NNK-induced SCEs	Lymphocytes exposed 3 h to NNK with washout and allowed to incubate for 40 h prior to harvest	1.4–2.3-Fold increase in SCE in combined variant allele groups when compared to wt (P < 0.05).	(S.Z. Abdel-Rahman, et al., 2000; Olshan, et al., 2002).
Arg399Gln **Arg/Arg (n = 208** **Arg/Gln (n = 237)** **Gln/Gln (n = 79)**	BPDE-induced chromosome. breaks/cell (b/c) Bleomycin-induced b/c	Lymphocytes exposed 24 h to BPDE without washout and b/c measured. Lymphocytes exposed 5 h to bleomycin without washout and b/c measured.	5% increase in b/c in Arg/Gln (P = 0.417)[c] 16% increase in b/c in Gln/Gln (P = 0.033)[c]. No difference seen in genotypes.	(Y. Wang, et al., 2003; Xiao, et al., 2016).
Arg399Gln[d] **Arg/Arg (n = 1)** **Gln/Gln (n = 1)**	Removal of CAA–DNA adducts.	Human lymphoblast cell lines exposed 1 h to CAA with washout to assess adduct removal 1 h post exposure.	Repair efficiency: 91% Arg/Arg. 22% Gln/Gln.	(Y Li, et al., 2006).
Arg399Gln **Arg/Arg (n = 33)** **Arg/Gln (n = 34)**	Repair of irradiation-induced DNA SSB.	Lymphocytes exposed 10 min to g-rays, lysed immediately or following 40min recovery period to measure SSB via comet assay.	SSB repaired/109 Da: Arg/Arg: 1.2 0.4 Arg/Gln: 0.9 0.5, P = 0.018 Gln/Gln: 0.6 0.5, P = 0.011	(P. Vodicka, et al., 2004; Hanssen-Bauer, et al., 2012).
Arg399Gln **Arg/Arg (n = 32)** **Arg/Gln (n = 25)** **Gln/Gln (n = 8)**	Repair of light-induced oxidative DNA damage.	HeLa cells pretreated with photosensitizer, irradiated with fluorescent lamp to induce 8-oxoguanines, then nuclei incubated with human lymphocyte extracts; removal of 8-oxoguanines measured by increase in SSBs	SSB/109Da: No difference seen across genotypes	(Y. Wang, et al., 2003; Ünal, et al., 2007).
Arg399Gln **Arg/Arg (n = 14)** **Arg/Gln (n = 21)** **Gln/Gln (n = 4)**	Repair of light-induced oxidative DNA damage.	Nuclei of HeLa cells pretreated with photosensitizer irradiated with halogen lamp for 3 min to induce 8- oxoguanines, then incubated for 10 min with lymphocyte extracts.	Rate of incision (arbitrary units)[e]: Arg/Arg- 137 Arg/Gln-125 Gln/Gln-40, P = 0.012.	(J. Slyskova, et al., 2007).
Arg399Gln **Arg/Arg (n = 24)** **Arg/Gln (n = 26)** **Gln/Gln (n = 11)**	Repair of X-ray induced DNA damage.	Lymphocytes from 61 volunteers were dosed with X-rays and then incubated for a 24 h recovery period to assess chromosomal aberrations	Chromosomal deletions: Arg/Arg: 14.8 1.2 Arg/Gln + Gln/Gln: 18.3 1.1.	(W.W. Au, et al., 2003; Sterpone, et al., 2010).
Arg399Gln **Arg/Arg (n = 33)** **Arg/Gln (n = 39)** **Gln/Gln (n = 8)**	Bleomycin-induced b/c	Lymphocytes exposed to bleomycin for 5 h without washout and b/c measured.	No significant difference seen across genotypes.	(J. Tuimala, et al., 2002).
Arg399Gln **Arg/Arg (n = 91)** **Arg/Gln (n = 95)** **Gln/Gln (n = 13)**	Bleomycin-induced micronuclei.	Lymphocytes exposed to bleomycin for 24 h without washout and frequency of micronuclei compared to cell line.	No significant difference seen across genotypes Baseline micronuclei higher in variants.	(S. Angelini, et al., 2008).
771> C **Not a population study**	Expression of reporter gene.	Reference or variant promoter transfected into different types of cultured cells.	Protein expression in variant 15–60% of reference sequence. Protein expression in variant 33% of reference sequence	(B. Hao, et al., 2006). (L. Liu, et al., 2010; Liu, et al., 2010).

Abbreviations: b/c, breaks per cell; wt, wild type; SSB, single strand breaks; Da, Daltons; CAA, chloroacetaldehyde, an active metabolite of vinyl chloride; BPDE, benzo(a) pyrene-diol-epoxide; NNK, nicotine-derived nitrosamine ketone; SCE, sister chromatid exchange.

a) Ref. (**Y. Wang, et al., 2003**) combined variant groups for analysis due to a homozygous variant frequency of 0.07 (n = 3) type.
b) Ref. (**S.Z. Abdel-Rahman, et al., 2000**) combined variant groups for analysis due to no difference being seen in NNK sensitivity within the homozygous and heterozygous cell lines.
c) Arg/Arg genotype as referent group.
d) Cells derived from 2 individuals, 107 cells for each line used in experiment.
e) Results estimated from visual inspection of box plots.

using this method by Angelini *et al*.[5]. Prior to harvest, lymphocytes were subjected to bleomycin for 24 hours and cultured for a total of 72 hours. To measure the number of spontaneous micronuclei, lymphocytes from a non-exposed control series were employed. Variant genotypes showed a little increase in spontaneous micronuclei (P = 0.04), but there was no variation in bleomycin-induced micronuclei between genotypes. [Table - 1]

Several investigations have examined the efficacy of repair and the ways in which XRCC1 SNPs modify its performance following the removal of the harmful material. To evaluate the elimination of DNA adducts, the experiment employed human lymphoblast cell lines from two individuals: one homozygous for the Arg399Gln locus (Gln/Gln) mutation and the other wild type[40]. The exposure of these two lymphoblast cell lines to vinyl chloride's reactive intermediate, chloroacetaldehyde (CAA), ultimately promotes BER. After washing away CAA from the culture media for one hour, the decrease in ethno-DNA adducts was used to measure the effectiveness of DNA repair [23,40]. To calculate the repair efficiency, one had to divide the total number of ethno-DNA adducts eliminated during the exposure period by the total number of adducts remaining at the end. The homozygous mutant cell line had a repair efficiency of only 22%, while the wild-type cell line had a repair efficiency of 91%. [Table -1]

Slyskova,[83] declared in his research that human cells have been used to assess radiation-induced DNA repair in connection to the Arg399Gln SNP. After 76 healthy people' isolated lymphocytes were exposed to grey radiation for 10 minutes, the comet assay was used to determine the quantity of SSB. The homozygous and heterozygous variants had significantly smaller numbers of single-strand breaks (SSBs), a measure of damaged nucleotide removal, per 109 Dalton, or the irradiation-specific DNA repair rate (P = 0.018 and P = 0.011), respectively.

The apparent gene-dosage effect is shown in Table-1, where the homozygous variant group shows a 50% loss in repair efficiency and the heterozygous variant group shows a 25% reduction. In an additional radiation-induced challenge test for DNA repair, chromosomal abnormalities were evaluated in the blood cells of 80 volunteers who received gamma radiation exposure in vitro and were given a 48-hour recovery period. The chromosome aberrations were caused by the radiation exposure, and the

Arg399Gln SNP made them even worse (18.3 vs. 14.8 aberrations in variant vs. wild type). The impact of the Arg399Gln polymorphism has also been assessed using the ability to eliminate 8-oxoguanine, a byproduct of oxidative DNA damage[7,42,67].

From the research of Vodicka *et al*.,[97] the impact of XRCC1 SNPs on DNA oxidative damage repair was also examined. According to their methodology, 8-oxoguanine was induced in HeLa cells by irradiating them after they had been treated with a photosensitizer. After the radiation, lymphocyte extracts from 65 patients were treated with the cell nuclei. To make the extracts, pure lymphocytes were lysed with Triton X-100, and the resulting supernatant-which contained DNA repair proteins-was separated from the nuclei and debris using centrifugation[63]. Since single strand breaks (SSBs) in HeLa cell DNA signify the removal of 8-oxoguanine by repair enzymes from the enzymatic extract, the quantity of SBBs was thought to be a proxy for DNA repair efficiency.

In another investigation, the Arg399Gln polymorphism categorisation was used to count HeLa cells cultivated with lymphocyte extracts from various patients in order to quantify SSB[97]. By first treating the HeLa cells with a photosensitizer and then irradiating them with halogen light, oxidative DNA damage was induced. Cell nuclei were incubated with lymphocyte extracts to begin DNA repair following the cessation of irradiation. The rate of incision in the homozygous Arg399Gln variant was shown to differ significantly (3.4-fold) from that of the wild-type ($P = 0.012$), but not in the heterozygous variant. At last, the impact of the Arg280His genotype on XRCC1's ability to repair DNA was the subject of two investigations. Based on the Arg280His genotype, the mean chromatid breaks per cell (b/c) in response to bleomycin were calculated using lymphocytes isolated from 80 participants. Prior to harvest, lymphocytes were exposed to bleomycin for the final five hours of incubation without washout, so there was no chemical-free interval during which damage could be observed to be repaired. Because of the low frequency of the homozygous variant ($n = 1$), breaks per cell were compared between the wild-type and a combined variant group. The variant group showed a 25% increase in the mean number of breaks per cell. [Table-1]

In a second investigation, cDNA encoding the wild type or variant versions of this gene was transfected into a mammalian cell line lacking in XRCC1, and the cells were subsequently cultured with DNA-damaging chemicals (hydrogen peroxide or methyl methane sulfonate) without any washout. Even though a crucial BER polymerase uses NADPH as a cofactor, the indirect indicator of strand break repair was observed when this cofactor was being depleted within cells. The genotoxic incubations did not cause NADPH depletion in cells carrying wt XRCC1, but the codon 280 (Arg) polymorphism was linked to a significant depletion and the codon 399 (Gln) polymorphism to a lesser depletion[65]. This implies that the codon 280 polymorphism has a higher impact on XRCC1 function, though the indirect measure of repair raises the possibility that the polymorphism may have affected NADPH levels through a different mechanism. The Arg280His variant reduced XRCC1's ability to bind to DNA but did not affect the other

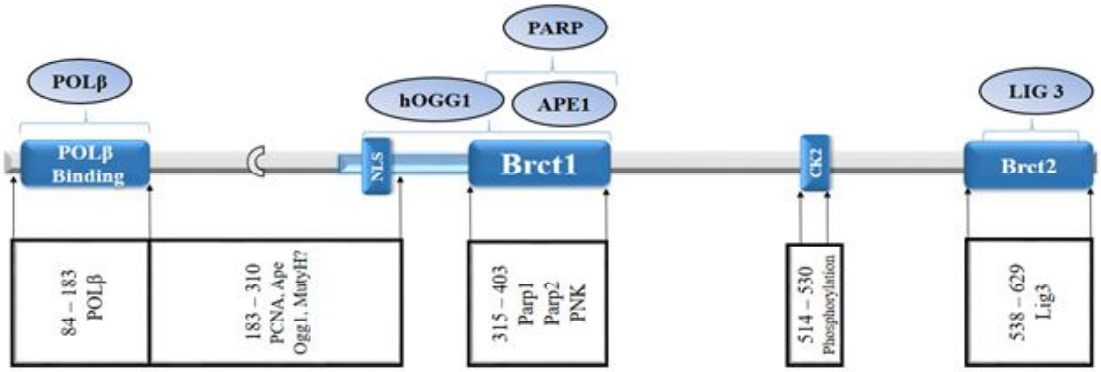

Figure-5. The human XRCC1 domain's positions that shows non-synonymous single-nucleotide polymorphisms (SNPs).

protein interactions. This was interpreted to mean that Arg280His is more likely to impair BER than is Arg399Gln or Arg194Trp. However, the relevance of this reconstituted in vitro system to the functioning of XRCC1 variants in vivo is uncertain. Nine XRCC1 variant proteins were synthesised in recombinant expression systems, and their DNA and protein binding properties were assessed[29].

Polymorphism effect on XRCC1 gene expression :

The analysis of the mRNA levels of XRCC1 in lymphoblastic cells from 28 individuals in a breast cancer registry revealed that higher gene expression was linked to the position 399 mutation (Gln). In contrast, the variant cells did not exhibit an increase in DNA repair activity. Since the polymorphism is in a structural area of the gene, which should theoretically influence enzyme activity but not gene expression, the consequences of the enhanced gene expression are unclear. It has been discovered that an upstream regulatory sequence region (77T > C; rs3213235) has a polymorphism sequence that binds the XRCC1 promoter[29].

Reduced gene expression is the result of a greater binding affinity between the Sp1 transcription factor and the XRCC1 promoter. In four distinct expression systems, XRCC1 promoter constructs containing either T or C at position 77 were transfected. The C variant's transcription activity ranged from 15% to 60% of that of the T (wild type). Upon transfection of MCF-7 cells with either the C variation or the reference XRCC1 promoter, the reference promoter facilitated three times as much reporter gene transcription as the C allele[29, 67,70].

Single nucleotide polymorphism (SNPs):

Despite single nucleotide polymorphisms (SNPs) being the most common type of sequence variation found in the genome, their use as genetic markers for understanding population evolution has only recently become evident. Because they are found throughout

the genome they are also suitable for investigating historical demography and speciation, especially in light of a recent theory that suggests that many unlinked gene are required to estimate population genetic parameters with statistical certainty[41,77].

Although SNPs have less variety than microsatellites, they should nonetheless make it easier to analyse the genetic diversities and histories of various species. Some recent studies shown that five additional non-synonymous SNPs have evolved, but none of

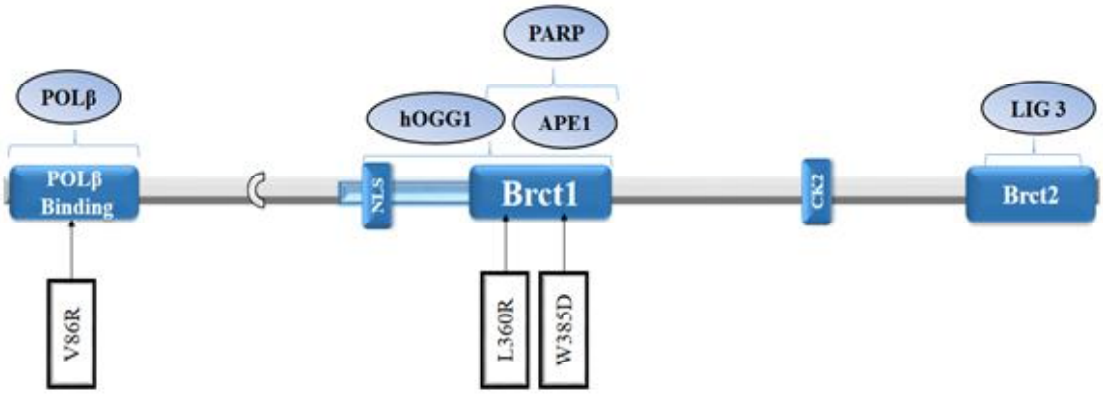

Figure - 6. Human XRCC1 domains and locations of three-point mutations shown to have an adverse effect on XRCC1 function.

them have been the subject of epidemiological research, and their prevalence rates are all less than 5%. Among them, P161L is the only one who'sin silico predictions indicate that it is potentially harmful and intolerant. It is located inside the Pol β binding domain [Figure - 5] and has the potential to impair this significant gene product's interaction function, this is not surprising. More research on P161L would be beneficial. Another SNP, Y576S, is located in the BRCT2 domain where XRCC1 connects with Ligase 3 and is expected to be probably harmful but tolerant[10]. [Figure -6]

Point mutations affect XRCC1 function :

In CHO cell lines, three-point mutations have been investigated and found to affect XRCC1 function. V86R is in the binding domain of Pol β [Figure -6] and entirely removes the XRCC1 NTD's binding to Pol β [24].

The mutation is in the five-stranded beta sheet of the core beta sandwich, and it interferes with a crucial hydrophobic interaction with the Pol β thumb loop without negatively impacting the folding of the NTD. This leads to a reduction in the efficiency of base excision repair. The third point mutation, W385D, also occurs in the BRCT1 domain and interferes with PARP1 binding[25]. These point mutations are not naturally occurring, but they are helpful in examining facets of XRCC1 function.

It has been demonstrated that XRCC1 contains a huge number of SNPs, and due to their relatively high frequency in the population, a number of these have been thoroughly examined in cancer epidemiology association studies. In a range of ethnic origins, association trends with particular cancer types have been observed; nevertheless, inconsistent findings have hindered the drawing of certain inferences. Most of the research has demonstrated that different genotypes of XRCC1 Arg399Gln, as well as Arg280His and Arg194Trp, can alter inter-individual susceptibility to different types of cancer in breast, lung, head, and neck. To explore the importance of SNPs in other cancer susceptibility, new model systems are needed, as their functional significance is still largely unknown. Newly developed mutant mouse lines that reflect human polymorphisms may offer a new generation of mammalian tools for carcinogen exposure studies related to human cancer.

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Conflict of Interest

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