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Association of DNA Repair XRCC1 Gene Polymorphism with Leukemia

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ABSTRACT

A group of cancerous diseases of the blood and bone marrow known as leukemias are life-threatening. It is crucial to recognize the leukemic cells lineage when making a diagnosis of leukemia because treatment for the disease depends on whether the cells are myeloid or lymphoid. As per the Observation There is total 300 blood samples in which 150 were leukemic patients and 150 were healthy person. The genotype distribution frequencies of the XRCC1 gene's SNP rs25487 results demonstrate a highly significant connection between heterozygous (GA) rs25487 of the XRCC1 gene and an increased risk of leukemia up to 2-folds (OR=2.52; 95% CI=1.51- 4.20; p=0.0004). The scenario is identical when it comes to homozygous mutant (AA), which also shown a highly significant connection with a reduced risk of leukemia and performs a protective role (OR=0.40; 95% CI=0.23-0.70; p=0.0014). The combined genotype model of mutant and hetero of rs25487 demonstrated a weakly non-significant correlation with leukemia (OR=1.14; 95% CI=0.72-1.82; p=0.5618). This study intended to look at the connection between leukemia risk regulation and XRCC1 polymorphisms, as well as the conceivable relationship between leukemia patients and the XRCC1 polymorphism (rs25487). It was determined that rs25487 was linked to a higher risk of leukemia in people.

INTRODUCTION

Leukemia is a blood-related cancer that has two features that are changing hematopoietic progenitors and extensive bone marrow infiltration (Soerjomataram et al., 2018). According to the cell that gave rise to them and the rate of proliferative growth, they can be categorized as acute, chronic, myeloid, or lymphoid depending on the condition. The two most frequent types of leukemia that affect the lymphoid chain are acute lymphoblastic leukemia (ALL) and chronic lymphocytic leukemia (CLL). Acute myeloid leukemia (AML) and chronic myeloid leukemia (CML), both of which affect the myeloid lineage, are the next two diseases. The World Health Organization (WHO) classification for acute leukemias and myeloid neoplasms was modified in 2016, resulting in several revisions to the previous classification (Arber et al., 2016). Leukemia development is linked to a variety of genetic and environmental danger factors. Multiple leukemia subtypes are connected to a higher risk of exposure to ionizing radiation (Ferlay et al., 2018). Acute leukemia is

more likely to develop later in life in people who have previously received chemotherapy, particularly those who received alkylating agents and topoisomerase II inhibitors (Kobetz et al., 2020). Certain ALL subtypes are related with the Epstein Barr infection, the human White blood cell leukemia infection, and viral contaminations (Davis et al., 2014). Among the hereditary issues related with an expanded gamble of fostering ALL and AML incorporate Li-Fraumeni condition, Blossom disorder, Fanconi paleness, and Down condition (Stieglitz et al., 2013). A history of any hematologic malignancy is connected to an increased danger of later developing another subtype of leukemia (friedman et al., 2010). Leukemia cases have increased due to lifestyle decisions like smoking, inactivity, eating foods high in energy, and some habits like the use of local and agricultural insecticides, living near busy roads, being exposed to benzene and other sources of low-frequency electromagnetic fields) (Demoury et al., 2007). A new report demonstrates that there might be acquired changes that raise the gamble of leukemia even without any extramedullary aggregates, in spite of the way that people with bone marrow disappointment issues, DNA fix imperfections, and sacred chromosomal peculiarities are inclined toward creating hematologic malignancies (Owen et al., 2007).

Purpose of study research's objective is to look into how the DNA repair gene XRCC1 polymorphism manifests itself in leukemia. The DNA damage response (DDR) signaling pathway is a well-organized network that eliminates replication errors (Nickoloff et al., 2011). Genomic instability caused by DDR dysfunction is considered one of the most important oncogenic mechanisms (Calzone et al., 2007). Cells have a number of DNA repair processes that eliminate many DNA damages in order to combat these lesions and maintain genomic integrity (Bolufer et al., 2006). As reported by Huang et al., 2017 XRCC1 (X- ray repair cross-complementing 1) is a protein-writing gene that interacts with a number of repair enzymes despite not having any enzymatic activity. XRCC1 is a component of all of these repair enzymes that can carry out enzymatic processes to repair DNA base excision and nucleotide excision damage. X-ray cross-complementing protein 1 (XRCC1) is a significant representative of the BER pathway and functions as a scaffold to recruit BER for operation or strand break repair (Niedergang, 2010). XRCC1 is concerned in the first steps of the BER pathway's recruitment of other BER proteins and aids in correcting mistakes made during DNA replication and recombination (Zavaglia et al., 2016). In XRCC1, more than 300 SNPs have been reported rs25489 (Arg280His), rs25487 (Arg399Gln), and rs1799782 (Arg194Trp) are the three most extensively researched polymorphisms in the gene's coding region (Rasouly et al., 2017). The chosen XRCC1 SNPs have the capacity to alter protein structure, which may reduce the efficiency of BER pathway enzymes. According to (Pittman, 2001) the goal of the current study was to look into any potential links between leukemia and polymorphisms in the BER pathway gene XRCC1.In a compound with DNA ligase III, XRCC1 participates in DNA mending. One of the many methods by which cells retain the integrity of their genetic information is DNA repair. Extrinsic DNA damage is brought on by environmental causes such chemicals, ionizing radiation, and UV light. In addition, endogenous causes such DNA harm can result from oxidative stress, alkylation, hydrolysis (deamination, depurination, and depyrimidination), as well as DNA base mismatches (Saitoh, 2016). The BER pathway is primarily used to remove DNA lesions like oxidized bases, alkylated bases. XRCC1 the X-ray cross-complementing gene 1, on chromosome 19's long arm, at position 19q13 the 633-amino acid XRCC1 protein is encoded by 17 exons and is located where it plays an essential scaffolding and multifunctional protein role in BER (Mitra, 2012). The DNA repair gene XRCC1 is linked to the SNP rs25487, also known as Gln399Arg. Allele encode amino acids Arg to Gln protein (Nelson et al., 2002). In the XRCC1 gene, there is a single nucleotide polymorphism (SNP) termed Arg399Gln. The XRCC1 gene participates in the base excision and nick repair pathways. The XRCC1 gene is crucial for repairing DNA damage brought on by alkylating chemicals, ionizing radiation, X-rays and gamma rays.

Enzymes include DNA polymerase, DNA ligase III and poly ADP-ribose polymerase (PARP). Three essential functional enzymes that are produced by the XRCC1 gene, which codes for

the XRCC1 protein (Audebert et al., 2004). Other BER proteins can interact with XRCC1 in a region that has biologically significant interactions, including gap-filling D-ribose polymerase, poly (ADP-ribose) polymerase 1 (PARP-1) and others (Caldecott et al., 2010) DNA ligase 3a (LIG3a), DNA 30-phosphatase (PNKP) and DNA polymerase (POLβ). According to research by (Chen et al., 2003) genetic variations have been shown to affect DNA repair function. If the ability to repair DNA is inadequate, it could lead to genetic instability and even carcinogenesis (Jiang, 2009). As a result, depending on how much the XRCC1 gene polymorphisms are changed, different populations have different hereditary susceptibilities to ALL. In other words, polymorphisms in the XRCC1 gene may be related to childhood ALL. Codon 399 (extron 10, G-A, Arg-Gln), codon 194 (extron 6, C-T, Arg-Trp) and codon 280 (extron 9, G-A, Arg-His) are three frequently occurring single nucleotide polymorphism (SNP) sites in the coding region of the XRCC1 gene, respectively (Canalle, 2011). The SNP rs25487 Arg399Gln, G>A substitution is one of the XRCC1 SNPs that has drawn the most attention, but there are conflicting views on its significance (Nedooshan et al. ,2017). Leukemia, along with other malignant blood diseases, is one of the biggest barriers to understanding and treating cancer in humans. Researchers are examining whether genomic sequencing of tumor cells can support physicians in deciding on the best therapeutic option for each patient (for example, chemotherapy, targeted therapy, stem-cell transplantation, or a combination of therapies).

Cancer research has the potential to change and save lives. The goal of leukemia research is to create safe and effective methods for preventing, detecting, diagnosing, treating, and eventually curing the disease cure the group of diseases we collectively refer to as cancer. Studies on leukemia look for and find more efficient ways to detect, diagnose, and treat cancer. These studies can be created in a variety of ways by medical professionals and scientists in order to address their questions. Medical institution trials seek to ascertain the effectivity and safety of new diagnostic or therapeutic approaches.Many factors are involved that cause leukemia like exposure to benzene, chemotherapy and genetics. The mortality rate due to leukemia has also been increasing day by day. Death rate in Pakistan has also been increase. In order to control the death rate in Pakistan due to leukemia we have to take some preventive measures to overcome this situation. That`s the reason researcher wants to work on leukemia to determine the initial cause of leukemia so death rate can be controlled.

Objective

1. To investigate the association between leukemia patients and the XRCC1 Polymorphism (rs25487)
2. To investigate the association of this polymorphism with different demographic parameters.

MATERIALS AND METHODS

Identification of Patients and Collection of Blood Samples (Patients and Controls)

Before blood test assortment, partnered emergency clinics had morals council endorsement. The review included 300 members altogether, 150 of whom were patients and 150 of whom were solid controls who were matched for age and orientation. Associated Medical clinic, Pinum Emergency clinic Faisalabad, Youngsters Medical clinic Lahore, and Jinnah Emergency clinic Karachi were the clinics from which the leukemia patients were assembled. Control tests were taken from an emergency clinic and an undefined area. People of any age, sexual orientations, and smoking situations with haphazardly chose as tests. Each understanding finished up a marked assent structure during the enrollment time frame. We had direct meetings with every patient to dive deeper into their socioeconomics and any previous tobacco utilization. Their examples (2-3 ml/individual) were taken in 5 ml vacutainers that contained EDTA. The University of Lahore's (UOL) laboratory, which is located on the Sargodha Campus, received the blood that had been drawn. Until further use, collected blood samples were stored in 4°C refrigerators.

DNA Extraction from Whole Blood

BJ-miniature lab in Rawalpindi, Pakistan, utilized a DNA extraction unit to play out the extraction cycle. 200µl of blood and 1 milliliter of cooled reagent A were consolidated by more than once flipping the cylinders. Then the mixture was spined

at 4000 rpm for the 15 minutes at the room temperature. Supernatant was discarded and added 900µl chilled reagent A, re-suspended the pallet by vigorous shaking by hands. Then it was spined at 4000 rpm for 15 minutes at room temperature. Supernatant was discarded and added 800 µl reagent A, then pallet was re-suspended by strongly trembling with hands. It was spined at 4000rpm for 15 minutes at room temperature. Supernatant was discarded- and added 200µl reagent B, 20µl Reagent C, and 10µl Reagent D. The pallet was re-suspended bay shaking and the vortex mixing. The mixture was incubated at 65℃ for the 2 hours or 37℃ for overnight.

Tube was set down on ice and 50 µl of reagent E was added, shaking tube strongly and set down on the ice for the 15 minutes. It was spined at 4000rpm for 15 minutes to pallet down on the ice for the 15 minutes. It was spined at 4000 rpm for 15 minutes to pallets down the salt and proteins. Supernatant was transferred in fresh properly labeled 1.5 microliter centrifuge tube. Equal volume of chilled reagent F was added and inverted the tube gently till the DNA is visible. It was spined at 8000rpm for 1 minute at room temperature. And then discarded the supernatant. 200 µl Reagent G was added and the vortex for 15 sec. Then spined at 8000rpm for 1 minute at room temperature, and threw away supernatant.200 ml Reagent H was added to it and vortex for 15 sec. Then spined at 8000 rpm for 1 minutes at room temperature. The supernatant was discarded and reagent I of 100 µl was added. Incubation at 72℃ for 30 minutes. I store DNA at -20℃. Reagent F was stored and Reagent D at -20℃. All the other Reagents can be stored at room temperature.

Extracted DNA Quantification

Gel electrophoresis was carried out for confirmation of presence of DNA, that is to analyses and evaluate exact amount of acquire DNA.

Gel Electrophoresis

A 1% agarose gel was used to validate the presence or absence of DNA. In which added 5-8 µl DNA was laden into wells accompanying 2 µl of 10 x loading. 100V and 500Ma was used for gel run for 25 minutes. Presence or absence of DNA bands was observed through trans illuminators.

Primer Designing for Selected Polymorphisms

The exact amplification was used to help draw the unique gene polymorphism primers, which were then validated by the primer 3 software, and NCBI. WR stands for a wild type reverse primer. MR denotes the drawn reverse primer for mutants with mismatches, while CF denotes the conventional forward primer. The following is a list of the SNP rs25487 primers' product size and annealing temperature.

Polymerase chain reaction (PCR)

RFLP-PCR that is allele specific was denoted for amplification of DNA specific regions.

Amplification Product Optimization

PCR condition was optimized for primers (WR and MR), alternative primer concentrations are used for each polymorphism, and annealing temperature and MgCI2 concentrated forms were used. 2% agarose gel was needed to confirm the PCR products, and when it is optimized, PCR profile was handed down for melting step of 94℃ for 5 min, repeated to 35 cycles for 45 sec at 94℃, 45 sec for annealing temperature, phase of extension at 72℃ for 7-10 min then holding at 4℃ after product optimization.

DNA Sample Amplification for The Patients and Controls

For the DNA tests, which included 150 patients and 150 solid controls, quality polymorphic intensification was played out; the enhancement response volume for every item was 10 µl. For the improvement and intensification of related quality items, the Quality Amp PCR framework 9700 (Applied Biosystem, USA) was assigned, and 96-well warm cyclers were utilized. The accompanying records the response blenders for wild and freak.

Statistical Analysis

Age and gender demographic parameters were expressed as Mean ± SD. The categories of the i.e., smoking status and family history of the demographic characteristics were indicated. Smokers/nonsmokers and with/without respectively. For XRCC1 gene, rs25487 allele frequencies and mutations and the genotypic patients and control were measured by Hardy-Weinberg law. For ODD ratio calculation, 95% CI and the other significance value of the P value were measured by using an online software of

MEDCALC®. MS Excel`s formulae were used for measurement of mean and standard deviation.

RESULTS

XRCC1 gene polymorphism analysis

PCR is used for identification of Single nucleotide polymorphism (SNP) are used for enquiry of XRCC1 in leukemic patients and controls group.

Demographic Parameter of Controls and Patients

Entire person include in this study were 300.In which 150 were leukemic patients and 150 were healthy person. A complete description of demographic features of leukemia patients and control were given in tables:

Age

The mean age of patients and healthy control was ± 38 years. Age was categorized in 2 groups; less than 38 years and more than 38 years. Around 37.33% of leukemia patients belongs to age group > 38 while 62.67 were <38 years. A non-significant association was noted among average age of patients and healthy controls. For >38 years (0R=0.81; 95% CI=0.81(0.5-1.30; P=0.39).

Gender

In patient's males and females were 58.00% and 42.00% respectively. While 59.33% people in control group were men and 40.67% were women. A non-significant association was noted among average gender of patients and healthy group (OR=0.94; 95% CI= 0.59-1.49; P=0.81).

Smoking Status

The nonsmoker's leukemia patients were 68%, compared to 32% of smokers. In the control group, 42% of people smoked whereas 58% did not. In accordance with these findings, there was a statistically non-significant correlation between the leukemia risk of patients and controls (OR=0.64; 95% CI= (0.40-1.04); p=0.07).

Family History

Family history is an essential and crucial factor in the study of leukemia patients. This study was conducted according to the family history of both healthy and diseased groups. In this study 60.67% of patients had family history while rest of 39.33% of patients had no family history. Likely 25.33% of healthy group had some family history and 74.67% were no involvement of family history. Statistically highly important association with increased risk of leukemia up to 5-folds (OR=4.54; CI = 2.77-7.44; p=0.0001).

Table 1

Comparison of different demographic parameters in controls and cases

Variables	Case (n=150)	Controls (n=150)	Adjusted Odds ratio (95% CI)	P-value
Age (Y) Mean ±SD 38				
<38, n (%)	94(62.67)	101(67.33)	0.81(0.50-1.30)	0.39
>38, n (%)	56(37.33)	49(32.67)		
Gender				
Male, n (%)	87(58.00)	89(59.33)	O.94(0.59-1.49)	0.81
Female, n (%)	63(42.00)	61(40.67)		
Smoking status				
Smokers	48(32.00)	63(42.00)	0.64(0.40-1.04)	0.07
Non-Smokers	102(68.00)	87(58.00)		
Family History				
With	91(60.67)	38(25.33)	4.54(2.77-7.44)	0.0001
without	59(39.33)	112(74.67)		

n=total number; p=x2-test, chi square test; AOR=adjusted odds ratio; CI=confidence interval

Association of XRCCI Gene with Leukemia

Table 4.2 displays the genotype distribution frequencies of the XRCC1 gene's SNP r25487. Results demonstrate a highly significant connection between heterozygous (GA) rs25487 of the XRCC1 gene and an increased risk of leukemia up to 2-folds (OR=2.52; 95% CI=1.51- 4.20; p=0.0004). The scenario is identical when it comes to homozygous mutant (AA), which also shown a highly significant connection with a reduced risk of leukemia and performs a protective role (OR=0.40; 95% CI=0.23-0.70; p=0.0014). The combined genotype model of mutant and hetero of rs25487 demonstrated a weakly non-significant correlation with leukemia (OR=1.14; 95% CI=0.72-1.82; p=0.5618).

Table 2
Allele and genotype frequencies of selected SNPs of XRCC1 in patients and controls

SNPs	Genotypes	Case, n=150(%)	Control, n=150(%)	OR (95% CI)	p-value
rs25487	GG	65(43.33)	70(46.67)	Ref (1)	
	GA	61(40.66)	32(21.33)	2.52(1.51-4.20)	0.0004
	AA	24(16.00)	48(32.00)	0.40(0.23-0.70)	0.0014
	GA+AA	85(58.67)	80(53.33)	1.14(0.72-1.80)	0.5618

OR, odd ration; CI, confidence interval; CI and p- value calculated by regression analysis

Association of XRCC1 Polymorphism with Gender

XRCC1 gene rs25487 of male heterozygous (GA) indicated highly significant association with increased risk of this disease by 2-folds (OR=2.47; 1.27- 4.81; p=0.0073). Male homozygous (AA) mutant of same SNP also indicates significant association but will decrease risk of leukemia disease (OR=0.45; 0.22-0.92; p=0.0301). In case of female heterozygous (GA) showed non -significant results (OR=0.70;0.28-1.71; p=0.4395). Female homozygous mutant (AA) showed non- significant association with decrease risk of this disease (OR=0.46; 0.20-1.09; p=0.0785).

Table 3
Association of XRCC1 polymorphism with gender

SNPs	Gender	Genotype	Patients n=150 (%)	Controls n=150(%)	OR (95% CI)	p-value
rs25487	Male	Overall	87(58.00)	89(59.33)	0.94(0.59-1.49)	0.81
		GG	37(24.67)	42(28.00)	Ref (1)	
		GA	35(23.33)	19(12.67)	2.47(1.27-4.81	0.0073
		AA	15(10.00)	28(18.67)	0.45(0.22-0.92)	0.0301
	Female	Overall	63(42.00)	61(40.66)		
		GG	26(18.00)	28(18.67)	Ref (1)	
		GA	26(16.67)	14(8.67)	0.70(0.28-1.71)	0.4395
		AA	11(6.67)	19(12.67)	0.46(0.20-1.09)	0.0785

OR, odds ratio; CI, confidence interval; OR, CI and p-value calculated by regression analysis

Association of XRCC1 Polymorphism with age

Leukemia is not significantly linked with the rs25487 of the XRCC1 gene age group ≤38years heterozygous (GA) with increased risk of leukemia up to 1-fold (OR=1.22; 0.71-2.09; p=0.4691). (OR=0.40; 0.20-0.81; p=0.0116) Homozygous mutant (AA) exhibited highly significant connection with decreased risk of this disease. Age group ≥38 indicated a significant connection between heterozygous (GA) and an up to 3-fold increase in illness risk (OR=2.71;1.13-6.52; p=0.0251). (OR= 2.45;1.20-5.00; p=0.0133) Homozygous mutant (AA) revealed non-significant connection with increased risk of this disease up to 2-folds.

Table 4
Association of XRCC1 polymorphisms with age

SNPs	Age years	Genotype / Alleles	Patients n=150 (%)	Controls n=150(%)	OR (95% CI)	p-value
rs25487	≤38	Overall	94(62.67)	101(67.33)	O.81(0.50-1.30)	0.39
		GG	41(27.33)	48(32.00)	Ref (1)	
		GA	38(25.33)	21(14.00)	1.22(0.71-2.09)	0.4691
		AA	15(10.00)	32(21.33)	0.40(0.20-0.81)	0.0116
	≥38	Overall	56(37.33)	49(40.67)		
		GG	24(16.00)	23(15.33)	Ref (1)	
		GA	23(15.33)	10(6.67)	2.71(1.13-6.52)	0.0251
		AA	9(6.00)	16(10.67)	2.45(1.20-5.00)	0.0133

OR, odds ratio; CI, confidence interval; OR, CI and p-value calculated by regression analysis

Association of XRCC1 Polymorphism with Smoking Status

Smoking history of individuals with heterozygous wild (GA) rs25487 demonstrated significant connection with increased risk of leukaemia up to 3-folds (OR=2.74; 1.18-6.34; p=0.0180).

Homozygotes (AA) with a history of smoking have a negligible correlation with a lower incidence of leukemia (OR=0.36;0.14-0.95; p=0.0080). Heterozygous (GA) demonstrated a very non-significant connection with an elevated risk of leukemia up to a 2-fold (OR=2.40; 1.26-4.58; p=0.0076) in other patients in whom smoking history is unrelated. (OR=0.41; 0.20-0.83; p=0.0135) Homozygous mutant (AA) demonstrated significant correlation with decreased incidence of leukemia.

Table 5

Association of XRCC1 polymorphisms with smoking status

SNPs	Smoking status	Geno-type / Alleles	Patients n=150 (%)	Controls n=150 (%)	OR (95% CI)	p-value
rs25487	Smokers	Overall	48(32.00)	63(42.00)	0.64(0.40-1.04)	0.07
		GG	21(14.00)	30(19.33)	Ref (1)	
		GA	20 (13.33)	13(8.67)	2.74(1.18-6.34)	0.0180
		AA	7(4.67)	20(13.00)	0.36(0.14-0.95)	0.0410
	Non-Smokers	Overall	102(68.00)	87(58.00)		
		GG	45(29.33)	41(27.33)	Ref (1)	
		GA	41(27.33)	19(12.67)	2.40(1.26-4.58)	0.0076
		AA	16(10.67)	27(18.00)	0.41(0.20-0.83)	0.0135

OR, odds ratio; CI, confidence interval; OR, CI and p-value calculated by regression analysis

Association of XRCC1 Polymorphism with Family History

Leukemia risk was non-significantly associated with homozygous mutant (AA) of rs25487 in patients' family histories (OR=0.42;0.17-1.03; p=0.0585). (OR=2.56;1.06-6.22; p=0.366) Heterozygous (GA) had a non-significant correlation with illness with increased risk of leukemia by 3-folds. In other patients, family history is not a factor, and homozygous mutant (AA) and heterozygous mutant (GA) showed highly significant association with decrease risk of this disease (OR= 0.38; 0.16-0.85; p=0.0197) and increased risk of this disease up to three folds, respectively.

Table 6

Association of XRCC1 polymorphism with family history

SNP	Family History	Genotype Alleles	Patients n=150 (%)	Control n=150 (%)	OR (95% CI)	P=value
rs25487	With Family History	**Overall**	91(60.67)	38(25.33)	4.54(2.77-7.44)	0.0001
		GG	39(26.00)	18(12.00)	Ref (1)	
		GA	37(24.67)	8(5.33)	2.56(1.06-6.22)	0.0366
		AA	15(10.00)	12((8.00)	0.42(0.17-1.03)	0.0585
	With Family History	**Overall**	59(39.33)	112(74.67)		
		GG	26(19.33)	52(34.67)	Ref (1)	
		GA	24(16.00)	24(16.00)	2.51(1.26-5.00)	0.0086
		AA	9(6.00)	36(24.00)	0.38(0.16-0.85)	0.0197

0R odds ratio; CI, confidential interval; OR, CI and p-value calculated by regression analysis.

DISCUSSION

Increased leukocyte counts in blood or bone marrow are a common symptom of leukemia (Juliusson et al., 2016). Leukemia still poses a serious threat to people's health and the prognosis is not encouraging. In accordance with calculations from (Sung et al., 2020). Leukemia will rank as the fifteenth and eleventh most normal reasons for malignant growth occurrence and disease related rate, separately, in 2020 with 474,519 new instances of malignant growth overall and 311,594 fatalities. Each year, there were 14 new instances of leukemia for each 100,000 people. There were six places of yearly mortality for each 100,000 people. Leukemia occurrence rates appear to be most noteworthy in the US contrasted with profoundly created areas of Australia, North America, and Europe. Each day, there is an expansion in the all-out number of passings, the death rate, and every one of the three. 2020 saw a total of 1,733,573 cancer cases in South Asia, 62,163 of which were leukemia-related. The highest incidence rates were recorded in Sri Lanka (4.1 per 1,000,000), followed by Bangladesh (1.8

per 1,000,000) and Pakistan (4.3 per 1,000,000). The lowest incidence rates were recorded in Bangladesh (1.8 per 1,000,000) and Nepal (2.0 per 1,000,000.

In contrast, 1,124,875 people passed away in 2020, and leukemia was responsible for 45,707 of those deaths (4.1% of all fatalities). Pakistan had the highest death rate (3.04 per 1,000,000), while Bangladesh (1.04 per 1,000,000) and Nepal (1.05 per 1,000,000) had the lowest rates. The incidence and mortality rates among adults between the ages of 60 and 85 are highest in every country but Nepal. Leukemia is one of the most serious cancers that affects people of all ages (Poran et al., 2023). Pakistan and Sri Lanka reported the highest incidence rates in South Asia (4 points 3 and 4 points 1, respectively), while Bangladesh, Nepal and Bhutan had lower mortality rates (1.8, 2.0 and 2.4 respectively), according to data. In 2020, northern America was home to about 26,941 leukemia mortality cases and 56,876 incidence cases of the disease (13 percent of the world's total and 13 percent of the world, respectively) (Dikshit et al. ,2015).

The motivation behind this study was to decide if leukemia and the single nucleotide polymorphism (SNP) rs25487 in the XRCC1 quality were connected. XRCC1 is fundamental for the base extraction fix (BER) pathway and moves with DNA polymerase beta, poly ADP ribose polymerase (PARP), and DNA ligase III (Zhang et al., 2006). The X-ray cross complementing group 1 enzyme is produced by the 33 kb long XRCC1 gene (Gene ID 37414; OMIM 21171001 and 21174504), which has 17 exons and is located at Chromosome 19q13.3 which is a component of the base excision repair pathway (Wang et al., 2015). Genetic instability and carcinogenesis are caused by XRCC1 polymorphisms that interfere with the protein's ability to interact with other enzymatic proteins. (Yazdi et al., 2014). The close connection between PARP1 activity and XRCC1 activity, as well as its crucial role in preventing hereditary neurodegenerative disease, are probably the most intriguing aspects of XRCC1 function that have recently come to light. When exposed to ionizing radiation or alkylating agents, DNA single-strand breaks can be effectively repaired by the protein encoded by this gene. The base excision repair pathway is facilitated by interactions between this protein and DNA ligase III, polymerase beta, and poly (ADP-ribose) polymerase. The processing of DNA during mitogenesis and recombination in germ cells may be affected. Patients with varying levels of radiosensitivity who carry a rare microsatellite polymorphism in this gene are more likely to develop cancer (Mohtasham et al., 2008). Through genotype analysis, it was discovered that XRCC1 indicates the presence of three genotypes at rs25487, which are GG, GA, and AA.

A right around two-crease expansion in the gamble of leukemia is related with the heterozygous genotype (GA) of the rs25487 SNP (OR=2.52;95% CI=1,552, 2,020; p=0.0004). The polymorphism rs25487 (Arg399Gln) lies in a non-moderated district that displays a huge cell cycle delay and a more prominent sister chromatid trade recurrence in light of ionizing radiation (Dunning et al., 2015). Our examination uncovered that the XRCC1 quality polymorphism rs25487 doesn't appear to be connected to thyroid disease in the Pakistani populace (Bashir et al., 2013). Our outcomes are predictable with other exploration in various gatherings that neglected to find a connection between thyroid disease and the rs25487 polymorphism (Miao et al., 2014).In the Saudi population, similar outcomes were seen with breast cancer (Alanazi, 2013). Koreans are more likely to develop stomach cancer (Jin et al., 2015). and pancreatic cancer in the Chinese population (Jiang et al., 2014).

This information indicates that rs25487 has no effect on patients with acute myeloid leukemia's overall survival. In homozygous mutant (AA) individuals, a highly significant association (OR=0.40; 95 percent CI=0.23-0.70; p=0.0014) is found along with a lower risk of leukemia. The findings of this study agree with those of (Sygut et al., 2013), who learn that rs25487 is a significant prognostic factor. It should be applied when stratifying patients with acute myeloid leukemia. The costive domain of PARP or polynucleotide kinase (PNK) becomes dysfunctional as a result of a missense mutation in exon 10 (codon 399) brought on by one of the most common polymorphisms of XRCC1 (rs25487; Arg399Gln), which can obstruct the repair procedure (Santana et al., 2017). According to studies, the XRCC1 rs25487 polymorphism is linked to a higher risk for a number of malignancy types. The conclusion

of(Sobiahe et al., 2020) and the results of our study are comparable.

In line with (Sobiahe et al., 2020), rs25487 is a poor prognostic and predictive section in skin cancer in patients who have received radiotherapy (Andreassen, 2005). During chemotherapy for ovarian cancer, some people with the wild G/G rs25487 genotype may develop severe neutropenia (Khrunin et al., 2010). In patients with breast cancer receiving radiotherapy, this genotype may also be linked to an increase in hematological toxicity (Petty et al., 2007). Additionally, skin cell toxicity increased (Gossage and Madhusudan, 2007). African-Americans had too little of the mutant A allele (15%) compared to other populations at the SNP rs25487 in XRCC1.

For the Arg399Gln polymorphism, the Turkish population, like other Caucasian and Asian populations, differs significantly from the African population. (Banescu, 2013) discovered that the XRCC1 gene's SNP rs25487 has been described. The XRCC1 polymorphism in Indian CML patients shows that the 399Gln and 194Trp alleles are connected with a higher probability of processing CML, especially in men over the age of 40. Understanding the cause and treatment of leukemia's in gene is crucial for understanding the importance of XRCC1 gene screening.

CONCLUSION

The research of my database identifies that XRCC1(rs25487) has a markedly increased risk of leukemia. Results demonstrate a highly significant association between heterozygous (GA) rs25487 of the XRCC1 gene and a high risk of leukemia by up to 2-folds (OR=2.52; 95 percent CI=1.51- 4.20; p=0.0004). The scenario is identical when it comes to homozygous mutant (AA), which also shown a highly significant connection (OR=0.40; 95% CI=0.23-0.70; p=0.0014). PCR was the technique used for analysis. Based on the findings, it was determined that rs25487 was linked to a higher risk of leukemia in people.

RECOMMENDATION

According to research findings, XRCC1 has a strong connection to leukemia and can lead to a number of genetic diseases that are blood-related, including head and neck cancer. To determine which specific SNP will serve as a biomarker tool to study the genetic causes of leukemia, more research should be conducted.

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