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Original Article

Prevalence of NER DNA repair gene XPG rs17655 C>G polymorphism among Saudi Populations: A Comparative Study with Global population

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ABSTRACT Environmental toxins damage DNA, increasing the risk of cancer if not repaired. Xeroderma pigmentosum group G (XPG) is essential for nucleotide excision repair (NER). The XPG exon 15 C>G polymorphism may influence this process, increasing the risk of cancer. We examined the frequency of the XPG exon 15 C>G polymorphism in the Saudi population and compared it with that in other populations.

By conducting a PUBMED search, we identified epidemiological studies across different ethnic groups. Allele and genotype frequencies were determined, and statistical analysis was performed using the SPSS 21 software. In Saudi Arabia, the frequency of the mutant allele G was 57%, which was higher than that reported in the USA, Brazil, and China. However, higher frequencies of G alleles were found in Germany (79%), India (65%), Italy (75%), Romania (78%), Spain (75%), and Tunisia (61%). The frequency of the GG genotype in Saudi Arabia was 32%, which was higher than that in the USA (5%), Brazil (12%), and other countries but lower than that in Germany, India, Italy, Romania, Spain, and Tunisia.

It was found that the XPG exon 15 C>G polymorphism has a unique frequency pattern in Saudi Arabia, probably due to ethnic differences. This study provided insights into the role of GG variants in the progression and therapeutic response of cancer, leading to improved treatments for the Saudi population.

Keywords: NER DNA Repair Genes, XPG, Polymorphism, Genotype, Saudi Population.

INTRODUCTION

Globally, cancer rates and fatalities are increasing rapidly, making cancer a public health concern (1). The incidence of cancer in the Saudi population is greater among those who lead sedentary lifestyles, consume processed meals, consume high-calorie foods, and smoke (2). Several factors are strongly associated with the development of cancer, including smoking, alcohol consumption, irregular lifestyles, genetics, and environmental factors; however, environmental carcinogens cause DNA damage, which may subsequently cause genomic instability and result in the development of cancer, and the molecular mechanisms underlying the genesis of cancer remain poorly understood. The DNA repair pathway may be affected by specific DNA repair gene polymorphisms, either by themselves or along with environmental factors, increasing an individual's chance of developing cancer. Knowing the genetic frequency of DNA repair gene polymorphisms in the population that affect cancer susceptibility may help researchers identify cancer, develop new therapeutic approaches, and predict the prognosis of this fatal illness.

The genetic DNA of organisms is continuously harmed by various external factors and byproducts of cellular metabolic processes, such as reactive oxygen species. DNA damage can result in mutations, genomic instability, and a greater risk of cancer if it is not repaired. Cells have developed intricate DNA repair processes to protect genome integrity and guarantee appropriate cellular function in response to these assaults (4). Deficiencies in genetic repair capabilities can affect how the body responds to chemicals that harm

DNA and aid in the onset or spread of cancer. Genes associated with DNA repair pathways are thought to be candidate genes for cancer susceptibility. "Polymorphisms in DNA repair genes may reduce the DNA repair capacity (DRC) of certain individuals compared to that of the general population." (5, 6). This emphasizes the importance of the genetic variables of hosts as determinants of individual DNA repair capability, which increases the susceptibility of the population to malignancy.

"Nucleotide excision repair (NER), an important DNA repair pathway, is an essential and adaptable system that tracks and fixes a range of DNA damage, such as bulky adducts, UV-induced cyclobutane pyrimidine dimers, and DNA cross-links" (7). Mutations in NER pathway genes may trigger changes in the risk of cancer. XPG is found on chromosome 13q22-q33 and encodes a structure-specific endonuclease with a length of 1,186 amino acids (8). This protein is essential for identifying DNA damage and attaches to and cleaves damaged DNA very early on to accelerate the process of DNA repair later. "Additionally, XPG is implicated in RNA transcription through interaction with other transcription activator complexes, which eventually influence mutagenesis and cell death" (9, 10). Single nucleotide polymorphisms (SNPs) in the XPG gene have been linked to an increased risk of developing different types of cancer in different populations.

A faulty XPG causes DNA repair issues, which in turn cause genomic instability, gene dysfunction, and the start of carcinogenesis (11). *XPG* is highly polymorphic. Among known polymorphisms, a nonsynonymous Asp1104His (C>G) polymorphism (rs17655) at codon 1104 in exon 15 may affect protein activity and interaction with TFIIH and XPG function, thereby affecting NER function and DRC and altering genetic integrity and susceptibility to cancer (12). Therefore, the onset and progression of cancer may be intimately associated with genetic changes in NER-related genes.

Interest in the molecular genetics of cancer in Saudi Arabia has increased in recent years, and several studies have focused on DNA repair genes. These findings suggest that the *XPG* gene may be a useful predictive molecular genetics biomarker for cancer. This study determined the prevalence of the *XPG* exon 15 C>G polymorphism in a normal healthy Saudi population and compared it to that reported in a sufficient number of epidemiological studies in other populations worldwide. This is the first study to compare the frequency of XPG exon 15 C>G DNA repair gene polymorphisms among the Saudi population and other populations worldwide.

MATERIALS AND METHODS

Subjects

Prevalence of gene variants

We searched MEDLINE and PUBMED by applying "*Xeroderma pigmentosum group G*", *"Excision repair cross-complementation group* 5", "XPG", "*XRCC5*", "polymorphism", "genetic variant", "cancer", and "carcinogenesis". There were no language restrictions, and the search was restricted to human topics. Only the genotype frequencies of the control population were considered for case-control investigations. We excluded articles that did not disclose genotype frequencies, only allele frequencies were included.

Statistical analysis

"Pearson's $\chi 2$ test was performed to compare the genotype and allelic frequencies of different populations using the SPSS software (version 21). Court Lab (web-based software) was used to examine the Hardy-Weinberg equilibrium. All results were considered to be statistically significant at $P < 0.05$.

RESULTS

We identified 15 publications (13–27) reporting the frequency distribution of the XPG exon 15 G>C polymorphism in different populations, which were subsequently compared to the Saudi population. The frequency distributions of three genotypes and alleles of the *XPG* exon 15 G>C gene polymorphism in different populations with reference to Saudi Arabia were compared via the $\chi 2$ test (Table 1). The variant genotype GG frequency in the Saudi population was 32%, which was higher than that in the USA (5%), Brazil (12%), China (20.4%), Czech Republic (4.3%), France (2%), Korea (28.6%), Poland (5%), and Turkey (9.4%). The frequency of the variant genotype GG was greater in Germany (62%), India (42%), Italy (56%), Romania (61%), Spain (55%), and Tunisia (36%) than in the Saudi Arabian population. A significant distribution of the variant genotype was noted in the USA, Brazil, Czech Republic, France, Germany, Italy, Romania, Spain, and Turkey compared to the Saudi Arabian population. However, no significant differences were found in China, India, Korea, or Tunisia. The frequency of the variant allele G in the Saudi Arabian population was 57%, which was higher than that reported in the USA, Brazil, China, the Czech Republic, France, Poland, and Turkey. However, the frequency of variant allele G was greater in Germany (79%), India (65%), Italy (75%), Romania (78%), Spain (75%), and Tunisia (61%) than in the Saudi Arabian population.

DISCUSSION

"Single-nucleotide polymorphisms (SNPs) are the most common form of variation in the human genome, which can alter the level of expression or function of genes or their encoded products and thus determine the phenotype of the organism" (28). "SNPs in DNA repair genes can influence the level of DNA damage, individual

DNA repair capacity (DRC), and cancer risk" (29). Consequently, SNPs are necessary for the mechanisms underlying cancer (30). “Many studies have shown that exposure to exogenous and endogenous carcinogens (DNA-damaging chemicals) as well as the genetic profile or “genetic makeup” of individuals determine their risk of developing cancer. This genetic susceptibility may result from inherited polymorphisms in genes involved in carcinogen metabolism and repair of DNA damage” (31).

“Damage identification, damage demarcation and unwinding, damage incision, and new strand ligation are the phases of NER. More than 30 components are involved in this intricate process, and each step requires corresponding functioning proteins” (32). “Polymorphisms of NER genes can further alter the NER process by influencing the expression and function of key proteins in the NER pathway. Thus, polymorphisms in the NER genes might be associated with genetic susceptibility, chemotherapeutic sensitivity, and the prognosis of cancer (33). Information from healthy individuals is needed to assess the significance of these genetic markers in the vulnerability, expression, prognosis, and treatment of illness because DNA repair gene polymorphisms are distributed significantly differently across different ethnic groups. Since ethnicity affects a person’s susceptibility to specific diseases, it is necessary to investigate how NER gene genotypes and minor alleles vary across different groups because these genes are essential for maintaining the accuracy of the genome.

In this study, the Saudi population had a 32% variant genotype GG frequency, which was higher than that found in the USA, Brazil, China, Czech Republic, France, Korea, Poland, and Turkey. However, compared to the Saudi Arabian population, individuals in Germany, India, Italy, Romania, Spain, and Tunisia had higher frequencies of the variant genotype GG. A significant frequency distribution of variant genotypes was found when the Saudi Arabian population was compared to the USA, Brazil, the Czech Republic, France, Germany, Italy, Romania, Spain, and Turkey. However, no significant findings were recorded in China, India, Korea, or Tunisia. The Saudi Arabian population has a 57% frequency of the mutant allele G, which is higher than that of the United States, Brazil, China, Turkey, Poland, France, and the Czech Republic. The variant allele G frequency was higher in Germany (79%), India (65%), Italy (75%), Romania (78%), Spain (75%), and Tunisia (61%) than in Saudi Arabia. Ethnic heritage affects a person’s vulnerability to certain diseases (36). Therefore, the effect of ethnicity is indicated by the variation in the NER gene XPG exon 15 C>G polymorphism in the Saudi population compared to other populations globally. Research on genetic variations can help identify key risk factors for exposure to contaminants and malignancies, which may have implications for future preventative and detection strategies. Several factors, including ethnic variance, study population heterogeneity, and variations in sample sizes, may contribute to the variations in allelic frequencies found among these investigations. Individual DNA repair SNPs may have a smaller increase or decrease in risk than high-penetrance cancer genes, but because they are highly prevalent in the general population, they may have significant implications for public health. Therefore, epidemiological studies on DNA repair polymorphisms based on ethnicity are crucial (34). To decrease the possibility of false-positive and false-negative outcomes, large and integrated analyses might be preferable. A risk factor in one community may not be applicable in another because the incidence of DNA repair polymorphisms varies by population. The establishment of clinical and epidemiological databases may be based on such research.

Table 1: Genotype and allele frequency distributions of *XPG* exon 15(rs17655) gene polymorphisms in various populations and p-values compared to those in the Saudi Arabian population.

Country	Total No.	Age (years), Mean age ±SD	CC (%)	CG(%)	GG(%)	p-value	Variant allele G	Reference
Saudi Arabia	100		18 (18)	50 (50)	32 (32)	Ref.	57	13
USA	219	49.3 ±15.2	127 (58)	80 (37)	12 (5)	<0.001	24	14
Brazil	208		109 (52.4)	74 (35.6)	25 (12)	0.048	30	15
China	176	58.8 ±9.1	78 (44.32)	62 (35.23)	36 (20.4)	0.752	38	16
Czech	532	57.4 ±12.8	356 (66.9)	153 (28.8)	23 (4.3)	<0.001	19	17
France	53		31 (58)	21 (40)	1 (2)	0.013	22	18
Germany	374		18 (4.81)	124 (33.16)	232 (62.03)	<0.001	79	19
India	288		37 (12.84)	129 (44.79)	122 (42.36)	0.132	65	20
Italy	250		15 (6)	94 (38)	141 (56)	0.001	75	21
Korea	311	60.5 ±9.9	90 (28.9)	132 (42.4)	89 (28.6)	0.844	50	22
Poland	100		64 (64)	31 (31)	5 (5)	0.010	21	23
Romania	533		30 (5.6)	173 (32.5)	330 (61.9)	<0.001	78	24
Spain	214	53.9 ±8.4	14 (6.5)	81 (37.9)	119 (55.6)	0.002	75	25
Tunisia	125		18 (14.4)	61 (48.8)	46 (36.8)	0.583	61	26
Turkey	96		43 (44.8)	44 (45.8)	9 (9.4)	0.008	33	27

CONCLUSIONS

To summarize, our study showed that Saudi populations differ from populations around the world in the frequency of the genetic variant of XPG exon 15 C>G. This polymorphism can reduce DRC among Saudi individuals, increase cancer susceptibility, and act as a biomarker for cancer risk. Understanding the prevalence pattern of NER gene polymorphisms may help clinicians provide a more accurate prognosis and help discuss the expected outcomes, risks, and treatment options with patients.

INFORMED CONSENT STATEMENT

Not required as this study has been done through laboratory-based software, such as SPSS 21, for allele and genotype frequency determination and statistical analysis.

AUTHOR CONTRIBUTIONS:

Conceived and designed the study and experiments: MW

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CONFLICTS OF INTEREST

None.

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