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# Association of PARP1 SNP (rs1136410) with Brain Tumor Risk: Insights from *Khyber Pakhtunkhwa*

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## Abstract

**Background:** Brain tumors are among the most complex and life-threatening malignancies, with limited understanding of their genetic etiology. Poly (ADP-ribose) polymerase 1 (*PARP1*) plays a critical role in DNA repair. The single nucleotide polymorphism (SNP) rs1136410 (A>G) in *PARP1*, which results in a Val762Ala substitution, has been suggested to alter *PARP1* enzymatic activity and potentially influence tumor development. However, its association with brain tumors remains underexplored particularly in the population of Khyber Pakhtunkhwa (KP), Pakistan. **Methods:** In this study, we enrolled 200 patients with brain tumors, along with an additional 200 individuals as controls. DNA was extracted using the phenol–chloroform method, followed by genotyping through the Amplification Refractory Mutation System–Polymerase Chain Reaction (ARMS-PCR). Statistical analysis was conducted using GraphPad Prism. **Results:** The genotypic distribution of rs1136410 in brain tumor patients and healthy individuals indicates that this SNP is significantly associated with brain tumors (Chi-square = 13.24, df = 2, p = 0.0013). The AA genotype was associated with a 77% increased risk of overall brain tumors (OR = 1.77, p = 0.0065), an 88% increased risk of glioma (OR = 1.88, p = 0.0159), and a 2.9-fold increased risk of meningioma (OR = 2.91, p = 0.0073). In contrast, the GG genotype was associated with a 63% decreased risk of overall brain tumors (OR = 0.37, p = 0.0011), an 84% decreased risk of glioma (OR = 0.26, p = 0.0019), and an 80% decreased risk of meningioma (OR = 0.21, p = 0.0217). Similarly, the A allele was associated with an increased risk of brain tumors (OR = 1.88, p = 0.0065), whereas the G allele was associated with a decreased risk (OR = 0.53, p = 0.0001). **Conclusion:** In conclusion, this study demonstrates that rs1136410 is significantly associated with brain tumor risk particularly with the glioma and meningioma subtypes underscoring the role of *PARP1* in brain tumor genetics and its potential as a therapeutic target.

**Keywords:** Brain tumor- *PARP1*- rs1136410 (A>G)- ARMS-PCR- Khyber Pakhtunkhwa

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## Introduction

A brain tumor refers to an abnormal and uncontrolled growth of tissue that arises within the cranial cavity, including the brain, cranial nerves, meninges, and pituitary gland [1]. Brain tumors are among the most challenging and lethal forms of cancer, contributing significantly to global morbidity and mortality [2, 3]. Although environmental factors are known contributors, genetic predispositions, particularly specific gene polymorphisms, have also been increasingly recognized as key determinants of brain tumor susceptibility [4, 5]. To preserve genomic integrity, various DNA repair pathways are responsible for correcting genetic damage. One such pathway is the base excision repair (BER) pathway. Mutations in genes involved in these repair mechanisms, if left unrepaired, may lead to carcinogenesis. [6].

In the BER pathway, *PARP1*, located on chromosome 1q41–42, comprises 23 exons and spans approximately 47.3 kb [7]. It encodes a nuclear protein consisting of both an N-terminal DNA-binding domain and a C-terminal catalytic domain [7]. The *PARP1* gene plays a critical role in several cellular processes, including DNA damage detection and repair, regulation of cell death pathways, and mitotic apparatus function [8].

Several single nucleotide polymorphisms (SNPs) have been identified in the *PARP1* gene. Among these, rs1136410 results in a valine-to-alanine substitution at codon 762 within the catalytic domain, leading to reduced poly (ADP-ribosyl)ation activity [9]. To date, multiple studies have investigated the role of rs1136410 in various cancers, including gallbladder, esophageal, breast, lung, and brain cancers [10-14, 1]. However, the association

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between the *PARP1* SNP rs1136410 and brain tumor risk in the Khyber Pakhtunkhwa (KP) population remains unexplored. This study aims to investigate the association between the *PARP1* SNP rs1136410 and brain tumor susceptibility in individuals from KP.

## Materials and Methods

*Ethical Approval*

All study procedures conducted in the Health Biotechnology Laboratory were ethically approved by the Departmental Ethical Review Board of Abdul Wali Khan University, Mardan (Reference Number: AWKUM-213).

*Subjects*

Blood samples were collected from a total of 400 individuals, comprising 200 brain tumor patients and 200 control subjects, at Irfan General Hospital in Peshawar, Khyber Pakhtunkhwa (KP), between June 2023 and April 2024. Patients whose diagnoses were confirmed by biopsy and who provided informed consent were included in the study. Patients without histopathological confirmation, those with mixed tumors, or those who declined to participate were excluded. Control group inclusion criteria required participants to have no history of radiation exposure and no family history of cancer. Structured questionnaires and informed consent forms were developed to record demographic and clinical data, including age, gender, smoking status, tumor type and grade. Blood samples were collected in 5 mL ethylenediaminetetraacetic acid (EDTA) tubes and stored at 4 °C prior to genomic DNA extraction.

*Genomic DNA Extraction*

Genomic DNA was extracted from blood samples using the phenol–chloroform method. The quality of the extracted DNA was confirmed by 1% agarose gel electrophoresis and quantified using a NanoDrop spectrophotometer (Nano-Q, Optizen, Daejeon, South Korea).

*Genotyping*

Genotyping of the *PARP1* SNP rs1136410 (A>G) was performed using ARMS-PCR with tetra primers, as listed in Table 1.

*Primer designing*

Primers were designed by first retrieving the *PARP1* gene sequence from NCBI. Two inner primers were manually designed to target the wild-type and mutant alleles, with allele-specific nucleotides placed at the 3′ end of each primer. Two outer primers were designed using the NCBI Primer-BLAST tool (https://www.ncbi.nlm.nih.gov/tools/primer-blast/). The length, GC content, and melting temperature of the inner primers were adjusted using OligoCalc (http://biotools.nubic.northwestern.edu/OligoCalc.html). The same website was also used to assess primer self-dimerization and hairpin formation. In-Silico PCR (https://genome.ucsc.edu/cgi-bin/hgPcr) was performed to evaluate primer specificity. The sequence and length of each primer, along with their corresponding amplicon sizes, are provided in Table 1.

*Primer's dilution*

Primers were ordered from Fine Biotech (UK) and received in lyophilized form at a concentration of 25 nmol. To prepare the stock solution, 250 µL of PCR-grade water was added, yielding a final concentration of 100 µM. A 10 µL aliquot of this stock solution was further diluted with 90 µL of PCR-grade water to obtain a 100 µL working solution with a final concentration of 10 µM.

*ARMS-PCR*

Genotyping of rs1136410 was performed using a Thermo Cycler T100 (Bio-Rad). A 20 µL PCR reaction mixture was prepared, consisting of 10 µL of PCR master mix, 2 µL of genomic DNA, 1 µL of outer primers, 1.5 µL of inner primers, and 3 µL of nuclease-free PCR-grade water. The thermal cycling conditions included an initial denaturation at 94 °C for 5 minutes, followed by 35 cycles of denaturation at 94 °C for 45 seconds, annealing at 58 °C for 1 minute, and extension at 72 °C for 1 minute. A final extension step was performed at 72 °C for 10 minutes, followed by a hold at 10 °C.

*Gel Electrophoresis of Amplified Products*

Amplified PCR products were separated by electrophoresis on a 2% agarose gel prepared in 1× TAE buffer using a Bio-Rad electrophoresis system. After electrophoresis, the gels were visualized under a UV transilluminator. A 100 bp DNA ladder (GeneRuler, Invitrogen) was used as a molecular size marker to confirm the expected size of the PCR amplicons.

*Statistical Analysis*

All statistical analyses were conducted using GraphPad Prism version 8.0.1 (GraphPad Software, San Diego, CA, USA). Genotype and allele frequencies of the *PARP1* SNP rs1136410 were calculated by direct counting. Associations between genotypes or alleles and brain tumor risk were assessed using the Chi-square ($\chi^2$) test or Fisher's exact test, as appropriate. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to evaluate the strength of association. Model-based analyses were performed under different genetic inheritance models, including dominant, recessive, and codominant

Table 1. Tetra-Primer Design for Genotyping rs1136410 (A>G)

| Primer | Sequence | Product Size Base Pair (BP) | Band |
|---|---|---|---|
| Outer forward | CAGCAATGTCCGGGAACTTGTT | 401 BP | Control |
| Outer reverse | GTTTGCCATTCACTGTGTTGGAC | | |
| Inner reverse | GCTCCTCCAGGCCAAGGC | 297 BP | G Allele (mutant) |
| Inner forward | AGCAGGTTGTCAAGCATTTCCA | 143 BP | A Allele (wild) |

frameworks, to further explore the relationship between *PARP1* rs1136410 and brain tumor susceptibility. Additionally, stratified analyses were performed based on tumor subtype and tumor grade to evaluate genotype-specific associations within these clinical categories. A p-value less than 0.05 was considered statistically significant.

## Results

This study included 200 brain tumor patients and 200 control participants. The demographic and clinical characteristics of all participants are summarized in Table 2.

*Demographic Data*

The median age of patients was 38.5 years (range: 4–76), while the median age of controls was 43.5 years (range: 18–75). Among the patients, 119 were male and 81 were female, whereas the control group included 97 males and 103 females. A total of 19 patients were smokers, compared to 11 individuals in the control group. Although the proportion of smokers was higher among patients, the difference was not statistically significant (Fisher's exact test, p = 0.1878; OR = 1.71; 95% CI: 0.82–3.82). Additionally, 11 patients (5.5%) reported a family history of cancer, and 8 patients (4.0%) had previous exposure to ionizing radiation. None of the control participants had a family history of cancer or prior exposure to ionizing radiation, in accordance with the inclusion criteria.

*Genotyping and Allelic Distribution of the PARP1 SNP (rs1136410) Among Brain Tumor Patients and Control Participants*

In this study, we evaluated the association between the *PARP1* SNP rs1136410 (A>G) and brain tumor risk using the Chi-square ($\chi^2$) test under a codominant model. The distribution of genotypes (AA, AG, GG) differed significantly between patients and controls. The Chi-square test yielded a value of 13.24 (degrees of freedom = 2), with a corresponding p-value of 0.0013, indicating a statistically significant association between rs1136410 and brain tumor susceptibility.

Under the homozygous dominant model, the AA genotype was associated with a 77% increased risk of brain tumors (OR = 1.77; 95% CI: 1.09–2.87; p = 0.0065). In contrast, under the homozygous recessive model, the GG genotype was associated with a 63% decreased risk of brain tumors (OR = 0.37; 95% CI: 0.20–0.67; p = 0.0011). However, in the heterozygous model, the AG genotype was not significantly associated with disease risk.

Similarly, the additive model showed a consistent pattern: the A allele was associated with an increased risk of brain tumors (OR = 1.88; 95% CI: 1.39–2.56; p = 0.0065), while the G allele was associated with a decreased risk (OR = 0.53; 95% CI: 0.39–0.72; p = 0.0001). The detailed genotype and allele frequency distributions, along with odds ratios and p-values for each

Table 2. Demographic and Clinical Characteristics of Study Participants

| Demographic data | Variables | Patients (N=200) | Controls (N=200) |
|---|---|---|---|
| Age | Median (range) | 38.5 (4-76) | 43.47 (18-75) |
| Gender | Males/Females | 119 (59.5%)/81 (40.5%) | 97 (48.5 %)/103 (51.5%) |
| | Yes | 19 (9.5%) | 11 (5.5%) |
| Smoking | No | 181 (90.5%) | 189 (94.5%) |
| Family History | Yes | 11 (5.5%) | 0 (0%) |
| | No | 189 (94.5%) | 200 (100%) |
| Ionizing radiation | Yes | 8 (4%) | 0 (0%) |

Table 3. Genotypic and Allelic Distribution of PARP1 SNP rs1136410 (A>G) in Brain Tumor Patients and Controls

| Statistical model | Genotypes | Patients (n=200) | Control (n=200) | OR; 95%CI; P-value | $\chi$2 Value |
|---|---|---|---|---|---|
| Co-Dominant Model | AA | 126 = (63%) | 98 = (49%) | | 13.24, 2 |
| | AG | 56 = (28%) | 60 = (30%) | p: 0.0013 | |
| | GG | 18 = (9%) | 42 = (21%) | | |
| Homozygous Dominant Model | AA | 126 = (63%) | 98 = (49%) | OR: 1.772; | |
| | AG+GG | 74 = (37%) | 102 = (51%) | 95%CI;1.091-1.656; p: 0.0065 | - |
| Homozygous Recessive Model | GG AA+AG | 18= (9%) | 42 = (21%) | OR: 0.3721; | |
| | | 182 = (91%) | 158 = (79%) | 95%CI;0.2006-0.6731; p: 0.0011 | - |
| Heterozygous Model | AG | 56 = (28%) | 60 = (30%) | OR: 0.9074; | |
| | GG+ AA | 144 = (72%) | 140 = (70%) | 95%CI; 0.5835-1.406; p: 0.7411 | - |
| Additive Model | A | 308 | 256 | OR: 1.883; | |
| | G | 92 | 144 | 95%CI; 1.385-2.556; p: 0.0001 | - |
| | G | 92 | 144 | OR: 0.5310; | - |
| | A | 308 | 256 | 95%CI; 0.3913-0.7222; p: <0.0001 | |

Table 4. Association of *PARP1* SNP rs1136410 (A>G) with Brain Tumor Subtypes

| Sub types | Genotypes | Patients | Control | OR; 95%CI; p-value |
|---|---|---|---|---|
| Glioma (n=90) | AA | 58 | 98 | OR: 1.886; 95%CI: 1.145 -3.108; p: 0.0159 |
| | AG | 26 | 60 | OR: 0.9479; 95%CI: 0.5547-1.662; p: 0.8902 |
| | GG | 6 | 42 | OR: 0.2687; 95%CI: 0.1170-0.6515; p: 0.0019 |
| | A | 142 | 256 | OR: 2.102; 95%CI: 1.386-3.145; p: 0.0003 |
| | G | 38 | 144 | OR: 0.4757; 95%CI: 0.3179-0.7213; p: 0.0003 |
| Meningioma (n= 38) | AA | 28 | 98 | OR: 2.914; 95%CI: 1.355-6.031; p: 0.0073 |
| | AG | 8 | 60 | OR: 0.6667; 95%CI: 0.3221-1.331; p: 0.3291 |
| | GG | 2 | 42 | OR: 0.2090; 95%CI: 0.04801-0.7901; p:0.0217 |
| | A | 64 | 256 | OR: 3.000; 95%CI: 1.569 to 5.828; P: 0.0005 |
| | G | 12 | 144 | OR: 0.3333; 95%CI: 0.1716 to 0.6374; p: 0.0005 |
| Pituitary Adenomas (n= 40) | AA | 24 | 98 | OR: 1.561; 95%CI: 0.8025-3.034; p: 0.2281 |
| | AG | 12 | 60 | OR: 1.000; 95%CI: 0.4805-2.067; p > 0.9999 |
| | GG | 4 | 42 | OR: 0.4180; 95%CI: 0.1528-1.160; p: 0.1262 |
| | A | 60 | 256 | OR: 1.688; 95%CI: 0.9906-2.881; p: 0.0703 |
| | G | 20 | 144 | OR: 0.5926; 95%CI: 0.3472-1.009; p: 0.0703 |

comparison, are summarized in Table 3.

*Association of PARP1 SNP (rs1136410) with Brain Tumor Subtypes*

To assess the association of the *PARP1* SNP rs1136410 (A>G) with histologically defined brain tumor subtypes, patients were categorized into four groups: gliomas, meningiomas, pituitary adenomas, and rare brain tumors. The rare brain tumor group included Schwannomas (n = 10), Medulloblastoma (n = 7), Ependymoma (n = 5), Epidermoid cyst (n = 2), posterior fossa tumors (n = 3), metastatic intracranial retinoblastoma (n = 1), Craniopharyngioma (n = 2), and Hemangioblastoma (n = 2).

Analysis revealed that the homozygous AA genotype was associated with an 88% increased risk of glioma (OR = 1.89; 95% CI: 1.15–3.11; p = 0.0159) and a 2.9-fold increased risk of meningioma (OR = 2.91; 95% CI: 1.36–6.03; p = 0.0073). However, no significant association was observed between the AA genotype and pituitary adenomas.

Conversely, the GG genotype was significantly associated with an 84% decreased risk of glioma (OR = 0.27; 95% CI: 0.12–0.65; p = 0.0019) and an 80% decreased risk of meningioma (OR = 0.21; 95% CI: 0.05–0.79; p = 0.0217). No significant association was found between the GG genotype and pituitary adenomas. The heterozygous AG genotype was not significantly associated with the risk of glioma, meningioma, or pituitary adenomas.

Similarly, allelic analysis demonstrated that the A allele was significantly associated with a 2.1-fold increased risk of glioma (OR = 2.10; 95% CI: 1.39–3.15; p = 0.0003) and a 3-fold increased risk of meningioma (OR = 3.00; 95% CI: 1.57–5.83; p = 0.0005), but not with pituitary adenomas. In contrast, the G allele was associated with a 53% decreased risk of glioma (OR = 0.48; 95% CI: 0.32–0.72; p = 0.0003) and a 63% decreased risk of meningioma (OR = 0.33; 95% CI: 0.17–0.64; p = 0.0005). No significant association was observed between the G allele and pituitary adenomas.

Associations between rs1136410 and rare brain tumor subtypes were not evaluated due to low sample size and histological heterogeneity. A detailed summary of genotype and allele distributions by tumor subtype, along with corresponding ORs and p-values, is presented in Table 4.

*Association of PARP1 SNP (rs1136410) with Brain Tumor Grades*

In this study, we also analyzed the association between the *PARP1* SNP rs1136410 and different histopathological grades of brain tumors. The analysis showed that the AA genotype was associated with an 82% increased risk of Grade I tumors (OR = 1.82; 95% CI: 1.10–3.01; p = 0.0290) and an 8.8-fold increased risk of Grade II tumors (OR = 8.85; 95% CI: 3.06–23.81; p < 0.0001).

The AG genotype was associated with an 87% decreased risk of Grade II tumors (OR = 0.13; 95% CI: 0.03–0.49; p = 0.0010), but a 2.3-fold increased risk of Grade IV tumors (OR = 2.33; 95% CI: 1.17–4.64; p = 0.0220).

The GG genotype was significantly associated with an 80% decreased risk of Grade II tumors (OR = 0.21; 95% CI: 0.05–0.79; p = 0.0217) and a 78% decreased risk of Grade IV tumors (OR = 0.22; 95% CI: 0.05–0.84; p = 0.0342).

Similarly, allelic analysis revealed that the A allele was associated with a 79% increased risk of Grade I tumors (OR = 1.80; 95% CI: 1.20–2.69; p = 0.0049) and a 6.5-fold increased risk of Grade II tumors (OR = 6.56; 95% CI: 2.83–14.28; p < 0.0001). In contrast, the G allele was associated with a 45% decreased risk of Grade I tumors (OR = 0.56; 95% CI: 0.37–0.83; p = 0.0049) and an 85% decreased risk of Grade II tumors (OR = 0.15; 95% CI: 0.07–0.35; p < 0.0001).

A detailed summary of genotype and allele distributions across tumor grades, along with corresponding odds ratios and p-values, is presented in Table 5.

Table 5. Association of *PARP1* SNP rs1136410 (A>G) with Different Grades of Brain Tumors

| Grades | Genotypes | Patients | Control | OR; 95%CI; p-value |
|---|---|---|---|---|
| Grade 1 (n= 88) | AA | 56 | 98 | OR: 1.821; 95%CI: 1.100-3.013; p: 0.0290 |
| | AG | 22 | 60 | OR: 0.7778; 95%CI: 0.4496-1.360; p: 0.4786 |
| | GG | 10 | 42 | OR: 0.4823; 95%CI: 0.2380-1.008; p: 0.0664 |
| | A | 134 | 256 | OR: 1.795; 95%CI: 1.202-2.687; p: 0.0049 |
| | G | 42 | 144 | OR: 0.5572; 95%CI: 0.3722-0.8319; p: 0.0049 |
| Grade 2 (n= 38) | AA | 34 | 98 | OR: 8.847; 95%CI: 3.060-23.81; p: <0.0001 |
| | AG | 2 | 60 | OR: 0.1333; 95%CI: 0.03087-0.4915; p: 0.0010 |
| | GG | 2 | 42 | OR: 0.2090; 95%CI: 0.04801-0.7901; p: 0.0217 |
| | A | 70 | 256 | OR: 6.563; 95%CI: 2.832-14.28; p: <0.0001 |
| | G | 6 | 144 | OR: 0.1524; 95%CI: 0.07003-0.3531; p: <0.0001 |
| Grade 3 (n= 38) | AA | 20 | 98 | OR: 1.156; 95%CI: 0.5746-2.379; p: 0.7256 |
| | AG | 14 | 60 | OR: 1.361; 95%CI: 0.6372-2.802; p: 0.4459 |
| | GG | 4 | 42 | OR: 0.4426; 95%CI: 0.1614-1.238; p: 0.1789 |
| | A | 54 | 256 | OR: 1.381; 95%CI: 0.8179-2.365; p: 0.2935 |
| | G | 22 | 144 | OR: 0.7243; 95%CI: 0.4228-1.223; p: 0.2935 |
| Grade 4 (n= 36) | AA | 16 | 98 | OR: 0.8327; 95%CI: 0.4136-1.725; p: 0.7178 |
| | AG | 18 | 60 | OR: 2.333; 95%CI: 1.170-4.643; p:0.0220 |
| | GG | 2 | 42 | OR: 0.2213; 95%CI: 0.05074-0.8422; p: 0.0342 |
| | A | 50 | 256 | OR: 1.278; 95%CI: 0.7476-2.209; p: 0.4224 |
| | G | 22 | 144 | OR: 0.7822; 95%CI: 0.4526-1.338; p: 0.4224 |

## Discussion

*PARP1* is a critical component of the BER pathway, playing a key role in cellular responses to DNA damage, including lesion formation, strand breakage, and oxidative stress [15]. Alterations in *PARP1* expression or function at the cellular level can activate downstream signaling pathways involved in either DNA repair or apoptosis [7]. Among the approximately 1,198 missense SNPs reported in the *PARP1* gene (https://www.ncbi.nlm.nih.gov/snp), rs1136410 (A>G) was selected for this study due to its position within the catalytic domain and its previously reported associations with multiple cancer types [10-14, 1].

In this study, we evaluated the association between *PARP1* SNP rs1136410 and brain tumor risk across multiple genetic models, tumor subtypes, and histological grades. Our findings demonstrated a statistically significant association between rs1136410 and brain tumor susceptibility, with specific genotypes contributing differentially to disease risk.

The Chi-square test revealed a significant association between rs1136410 and overall brain tumor risk. The wild-type AA genotype was associated with an increased risk, whereas the homozygous GG genotype was associated with a decreased risk. Interestingly, the heterozygous AG genotype showed no significant association with overall brain tumor risk (Table 3). These results suggest that the A allele may increase susceptibility to brain tumors, while the G allele may confer a protective effect. These results are consistent with previous studies reporting a protective role of the G allele in acoustic neuroma [16], glioma [17] and glioblastoma [18]. However, they contrast with findings from several other studies, in which the G allele of rs1136410 was associated with an increased risk of gallbladder cancer [12], esophageal squamous cell carcinoma [13], brain tumors [1], thyroid carcinoma [19], lung cancer [20], cervical cancer [21] and breast cancer [15]. These discrepancies highlight the complex and possibly tissue-specific role of rs1136410 in cancer biology.

In the subtype analysis, the AA genotype was significantly associated with an increased risk of both glioma and meningioma, while the GG genotype was significantly associated with a reduced risk of these tumor types. No significant association was observed for pituitary adenomas (Table 4). These results suggest that rs1136410 may exert a tumor-specific effect, particularly in gliomas and meningiomas, which are known to exhibit distinct molecular and genetic features [2]. Our results are consistent with previous studies reporting a protective role of the G allele in glioma [17] and glioblastoma [18]. However, they contrast with other findings where rs1136410 was associated with an increased risk of glioma [1].

In the grade-wise analysis, the rs1136410 polymorphism showed a significant association with brain tumor severity. The AA genotype was associated with an increased risk of both Grade I and Grade II tumors, including an approximately 8-fold higher risk for Grade II tumors. In contrast, the GG genotype was significantly associated with a reduced risk of Grade II and Grade IV tumors. The AG genotype was linked to a decreased risk of Grade II tumors but an increased risk of Grade IV tumors (Table 5).

These findings suggest that rs1136410 may play a

significant role in brain tumor progression, with its impact differing by tumor subtype and histological grade. This underscores the importance of genetic predisposition within the molecular context of individual tumor types and highlights the need for further functional studies to elucidate the role of *PARP1* across diverse tumor subtypes and grades.

According to Wang et al. [9], the GG genotype is associated with reduced *PARP1* enzymatic activity. Although their study did not focus on brain tumors, this observation raises the possibility that reduced *PARP1* activity may play a protective role in brain tumor biology. However, this remains speculative in the context of the present study and requires experimental validation. Targeting *PARP1*, a key enzyme involved in DNA repair, may offer therapeutic potential, particularly for patients with gliomas and meningiomas. Notably, *PARP1* inhibitors such as olaparib, rucaparib, niraparib, and veliparib have shown promise in disrupting DNA repair mechanisms in various cancers, including brain tumors. Veliparib, in particular, is currently being investigated in clinical trials for glioblastoma and other central nervous system (CNS) malignancies [22].

Our findings demonstrate a statistically significant association between *PARP1* SNP rs1136410 and brain tumor risk. The GG genotype was associated with a decreased risk of brain tumors, particularly in glioma and meningioma subtypes, while the AA genotype appeared to increase susceptibility. Furthermore, this polymorphism showed grade-specific associations, suggesting a potential role in tumor progression.

Nevertheless, several limitations must be acknowledged. First, the samples were collected from a single center, which may limit the generalizability of the results. Second, the small sample sizes for certain tumor grades, particularly Grade II, and for rare tumor subtypes reduce statistical power and increase the likelihood of both type I and type II errors. Environmental factors, gene–gene interactions, and treatment histories were also not assessed in this study.

Future studies should include larger and more diverse populations to improve statistical validity and enhance generalizability, especially for less common tumor grades and histological subtypes. Functional investigations are also needed to clarify the molecular mechanisms by which rs1136410 may influence *PARP1* activity and contribute to brain tumor biology.

While our findings suggest potential clinical relevance for *PARP1*-based therapeutic strategies, particularly in patients with gliomas and meningiomas carrying the high-risk AA genotype, this must be interpreted with caution. Hypotheses about the protective role of reduced *PARP1* activity should be tested through mechanistic and functional studies.

In conclusion, this study provides evidence that *PARP1* SNP rs1136410 is significantly associated with brain tumor risk, with the A allele contributing to increased susceptibility and the G allele appearing protective. These associations were especially prominent in glioma and meningioma subtypes and varied by tumor grade. The results underscore the role of *PARP1* in brain tumor genetics and support its potential as a biomarker and therapeutic target. Further research is essential to validate these findings and investigate the underlying biological mechanisms.

## Author Contribution Statement

All authors contributed equally in this study.

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*Approval*

The study was approved by the Graduate Studies Committee of the Department of Biotechnology, Abdul Wali Khan University Mardan, Pakistan.

*Ethical Declaration*

Ethical approval for this study was obtained from the Departmental Ethical Review Board of Abdul Wali Khan University Mardan, Pakistan (Reference No: AWKUM-213). All procedures involving human participants were conducted in accordance with institutional ethical standards and relevant national guidelines.

*Conflict of Interest*

Nill.

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