Astana Medical Journal
e2790-1203

https://doi.org/10.54500/2790-1203-2025-4-125-amj001

Mutational Landscape of DNA Damage Response Pathways in Kazakhstani Children with Medulloblastoma

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Received: 10.03.2025
Accepted: 12.05.2025
Published: 30.08.2025

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Citation: Astana Medical Journal, 2025, 125 (4), amj001.

Abstract

Background. Medulloblastoma (MB) is the most common malignant pediatric brain tumor, and alterations in DNA damage response (DDR) genes may influence tumorigenesis, treatment response, and prognosis. However, the landscape of DDR mutations in Central Asian pediatric populations remains unexplored.

Methods. We performed a retrospective analysis of 42 pediatric MB samples collected from the "University Medical Center" Corporate Fund (Kazakhstan) between 2015 and 2024. DNA extracted from formalin-fixed paraffin-embedded (FFPE) tumor tissues underwent whole-exome sequencing with targeted analysis of 52 DDR pathway genes. Variants were classified per ACMG guidelines, and correlations with clinical data were evaluated.

Results. Pathogenic or likely pathogenic DDR gene mutations were identified in 71.4% of cases, with a predominance of homologous recombination (HR) and mismatch repair (MMR) pathway alterations. Frameshift and nonsense mutations were the most frequent types. Commonly mutated genes included ERCC6, SLX4, FANCM, and PMS1. Functional sensitivity analysis suggested that HR and nucleotide excision repair (NER) pathway mutations may confer increased susceptibility to cisplatin and etoposide. No significant associations were found between DDR status and survival or tumor stage overall; however, the total number of DDR variants negatively correlated with tumor stage ($r = -0.436$, $p = 0.019$), and translesion synthesis (TLS) pathway variants correlated positively with metastasis ($r = 0.346$, $p = 0.045$).

Conclusions. This study demonstrates a high prevalence of DDR gene mutations among pediatric MB patients, highlighting the potential clinical relevance of DDR alterations for risk stratification and personalized therapeutic strategies. The findings support the integration of DDR profiling into future MB research and treatment planning.

Keywords: medulloblastoma, DNA damage response, pediatric brain tumor, mutations, precision medicine.

1. Introduction

Medulloblastoma (MB) is the most common malignant brain tumor in children [1]. Due to its embryonal origin and high aggressiveness, MB tends to progress rapidly and frequently metastasizes through the cerebrospinal fluid pathways [2]. It accounts for approximately 18-25% of all pediatric brain tumors, and the five-year survival rate varies widely (from 20% to over 90%), depending on multiple factors such as patient age, presence of metastases, molecular subgroup, and other cytogenetic abnormalities [3]. Effective treatment of MB requires a multidisciplinary approach, typically involving a combination of surgery, radiotherapy, and chemotherapy [4]. However, treatment-related long-term adverse effects, such as neurocognitive decline, endocrine dysfunction, and secondary malignancies remain a significant concern, especially for long-term survivors.

The term medulloblastoma was formally introduced in 1925 by neurosurgeons Cushing and Bailey, who, upon analyzing approximately 400 cases of gliomas, identified 29 tumors localized in the cerebellum, predominantly in children (aged 2 to 28 years, with a mean age of 8 years) [5]. These neoplasms exhibited histological features distinct from those of gliomas and neuroblastomas, which prompted the authors to classify them as a separate entity and to propose the new term medulloblastoma.

The marked variability in clinical presentation and outcomes among patients with medulloblastoma, even in the context of histologically similar tumors, led to the hypothesis of underlying molecular heterogeneity in this disease. In 2010, a consensus conference held in Boston resulted in the classification of medulloblastoma into four molecular subgroups with distinct genetic characteristics: WNT (Wingless), SHH (Sonic Hedgehog), Group 3, and Group 4 [6,7]. These subgroups differ not only in their genetic profiles, but also in prognosis, treatment responsiveness, and relapse rates. In 2016, with a subsequent update in 2021, the World Health Organization (WHO) introduced a molecular classification of pediatric medulloblastoma that formally incorporated these four subgroups. They also show profound differences in biological behavior and clinical outcomes. WNT-subgroup tumors are associated with excellent prognosis (five-year survival >90%), while Group 3 tumors often exhibit MYC amplification, early

metastasis, and poor outcomes (five-year survival ~50%) [8]. The SHH subgroup has an intermediate prognosis, which worsens substantially in the presence of TP53 mutations. The 2021 WHO framework now recommends reporting both histological and molecular classifications to guide risk-adapted therapy [8,9].

Despite significant advances in molecular subgrouping of medulloblastoma (MB), the role of DNA damage response (DDR) pathways in MB pathogenesis and therapeutic resistance remains underexplored, particularly in pediatric cohorts. DDR mechanisms encompassing homologous recombination (HR), non-homologous end joining (NHEJ), mismatch repair (MMR), and base excision repair (BER) are critical for maintaining genomic stability and for the effectiveness of DNA-damaging therapies. Standard treatments for MB (surgery followed by craniospinal irradiation and multi-agent chemotherapy) exert their effects largely by inducing DNA damage (double-strand breaks from radiation, alkylation adducts from chemotherapy); tumor cells rely on DDR pathways such as HR/NHEJ for double-strand break repair and BER/NER (nucleotide excision repair) for adduct repair to survive these insults. Consequently, defects or alterations in key DDR genes can influence both tumor development and treatment response. Disruption of DDR genes such as TP53, ATM, ATR, BRCA1/2, and PARP1 contributes to oncogenesis and has been linked to radioresistance and chemoresistance in MB cells [10-12]. For example, TP53 (encoding the "guardian of the genome" p53) is mutated in a subset of MB and when inactivated leads to impaired DNA damage-induced apoptosis; TP53 mutations in MB (particularly the SHH subgroup) are associated with significantly worse outcomes due to defective p53-dependent cell death after therapy. Notably, in the SHH subgroup of MB, TP53 mutations are enriched in the SHH-α subtype and correlate with poor prognosis [4,12].

Alterations in other DDR components also have important therapeutic implications. Although loss-of-function mutations in homologous recombination (HR) repair genes such as BRCA2 or RAD51 are rare in medulloblastoma, they may render tumor cells particularly vulnerable to poly(ADP-ribose) polymerase (PARP) inhibitors through the principle of synthetic lethality. In HR-deficient tumors, the inability to accurately repair double-strand DNA breaks shifts the burden of repair to alternative pathways such as PARP-mediated single-strand break repair, thereby creating a therapeutic opportunity. This concept, supported by findings in other cancer types, suggests that HR-deficient tumors are significantly more sensitive to PARP inhibition. Conversely, upregulation of DDR pathways can promote resistance to conventional therapies. For instance, overexpression of checkpoint kinases (e.g., ATR/Chk1) or enhanced non-homologous end joining (NHEJ) activity may facilitate the rapid repair of DNA lesions, diminishing the efficacy of DNA-damaging agents. Inhibition of such pathways has been shown to sensitize tumor cells to radiation and chemotherapy. PARP1, a key sensor and mediator of single-strand break repair, has emerged as a notable DDR-related protein in medulloblastoma. Elevated PARP1 expression has been reported in various pediatric brain tumors, including MB, and has been associated with more aggressive tumor biology and inferior survival outcomes.

These observations have led to increased interest in PARP1 both as a therapeutic target and as a potential biomarker for predicting response to DNA repair-targeted therapies. Preclinical studies have demonstrated that pharmacological inhibition of PARP1 – such as with Olaparib – can sensitize medulloblastoma cells to ionizing radiation, enhancing DNA damage accumulation and promoting tumor cell death when used in combination. Furthermore, high levels of PARP1 expression in tumor tissue have been proposed as a predictive marker of responsiveness to PARP inhibitors, based on the premise that tumors with elevated reliance on PARP-mediated repair are more susceptible to its inhibition.

Current early-phase clinical trials are evaluating PARP inhibitors in pediatric brain tumors, and there is growing rationale for combinatorial strategies that pair PARP inhibition with checkpoint kinase inhibitors or cytotoxic chemotherapy to overcome resistance mechanisms.

To date, the mutational landscape of DDR-related genes in pediatric medulloblastoma remains insufficiently characterized in many populations,

especially in low- and middle-income countries. Large-scale genomic studies of MB have predominantly focused on North American, European, and East Asian cohorts, leaving regions like Central Asia underrepresented in international cancer genomics consortia. For example, Kazakhstan has had only limited reporting of pediatric MB genetics in the literature, and comprehensive profiling of DDR pathways in this population is lacking. Elucidating DDR gene alterations in understudied groups is not only important for understanding tumor biology but also has practical implications for patient care. Identification of mutations in genes like TP53, ATM/ATR, or HR pathway members in a given patient's tumor could enhance risk stratification and refine prognostication (e.g. TP53-mutant SHH MB might be flagged as high-risk requiring intensified therapy or novel agents) [4,12]. Likewise, recognizing a DDR deficiency (such as a BRCA pathway defect or mismatch repair deficiency) could support the integration of precision oncology approaches, guiding use of targeted treatments like PARP inhibitors or DNA damage checkpoint inhibitors for those who are most likely to benefit. Overall, a better characterization of the spectrum of somatic (and potential germline) DDR gene mutations in Kazakhstani children with medulloblastoma will fill a critical knowledge gap and can inform future personalized therapy. This study aims to perform such molecular profiling using contemporary genomic technologies, with the goal of improving outcomes by tailoring treatments to the tumor's DDR profile.

Therefore, this study aimed to comprehensively characterize the mutational landscape of DNA damage response (DDR) pathway genes in pediatric medulloblastoma patients from Kazakhstan using whole-exome sequencing of tumor samples. We further sought to analyze the distribution and types of DDR gene alterations, assess their potential associations with clinical features, and explore their predicted impact on sensitivity to DNA-damaging chemotherapeutic agents. By elucidating the DDR mutation profile in this cohort, we aimed to provide insights that may inform future risk stratification and guide the development of personalized therapeutic approaches for medulloblastoma.

2. Materials and Methods

Study Design and Patient Cohort

This was a retrospective cohort study including pediatric patients diagnosed with medulloblastoma who were hospitalized between 2015 and 2024 at the "University Medical Center" Corporate Fund, Kazakhstan. Diagnosis of medulloblastoma was histologically confirmed in all cases according to WHO classification criteria.

A total of 42 formalin-fixed paraffin-embedded (FFPE) tumor samples were collected and analyzed for the mutational landscape of DNA damage response (DDR) pathway genes. Clinical and demographic data, including age at diagnosis, sex, tumor stage (T0–T4), metastasis status (M0–M3), and survival status (alive or deceased during the study period), were collected where available. Correlation analyses between identified genetic alterations and clinical parameters were performed in a subset of 34 patients due to incomplete clinical data for the remaining eight cases.

All procedures involving human participants were conducted in accordance with institutional ethical standards and the Declaration of Helsinki. Informed consent for genetic analysis and use of clinical data was obtained from the patients' legal guardians.

Sample Collection and DNA Extraction

Archived FFPE tumor material was used for molecular genetic analysis. Sample selection was performed based on the preservation of morphological structure and the availability of sufficient tumor tissue. Inclusion in the study was based on a histologically verified diagnosis. Genomic DNA was extracted from FFPE samples using the ReliaPrep FFPE gDNA Miniprep System (Promega) following the manufacturer's instructions. The procedure included deparaffinization

using mineral oil (300-500 µL, depending on section thickness), incubation at 80 °C for 1 minute with mixing, followed by lysis with proteinase K buffer (200 µL buffer and 20 µL enzyme) at 56 °C for 1 hour and subsequently at 80 °C for 4 hours to reverse formalin-induced cross-links. After cooling, RNA was removed by treatment with RNase A (10 µL) at room temperature for 5 minutes. DNA purification was performed using columns with final elution in 30-50 µL of buffer.

The concentration and purity of the extracted DNA were assessed using a NanoDrop spectrophotometer (Thermo Fisher Scientific), calculating the optical A260/A280 ratio. DNA integrity and fragmentation were further evaluated by gel electrophoresis (1.5% agarose gel, 1×TAE buffer), with results documented using the I-BRIGHT GelDoc imaging system (Thermo Fisher Scientific). Fluorometric quantification was performed using the QuantiFluor dsDNA System (Promega) on a Victor Nivo Multimode Microplate Reader (PerkinElmer), and the DNA integrity number (DIN) was determined using the Agilent TapeStation 4200. The DNA concentration ranged from 2.2 to 331 ng/µL, with total yields between 0.05 and 8.5 µg. The DIN values for most samples ranged from 1 to 3.2, which is typical for FFPE-derived DNA. All samples passed quality control and were approved for subsequent library preparation and sequencing.

Whole-Exome Sequencing (WES*)*

Library preparation and exome capture were performed using the Twist Human Core Exome 2.0 (FFPE) kit (Twist Bioscience), following the manufacturer's standard protocol. A total of 50 ng of genomic DNA was used for library construction. DNA was enzymatically fragmented to a peak fragment size of approximately 200 base pairs.

The resulting libraries were indexed using TruSeq-compatible adapters, amplified, and subjected to quality control assessment using the Agilent TapeStation system and quantitative PCR with the KAPA Library Quantification Kit. Hybridization and target region capture were performed according to the Twist Bioscience protocol. Sequencing was carried out on an Illumina platform using a paired-end mode with a read length of 2 × 151 base pairs.

Bioinformatics Analysis

Primary data processing (basecalling) was performed using bclconvert software. Quality control of raw reads was assessed with FastQC. Sequence reads were aligned to the human reference genome GRCh38 (NCBI, February 2022 release) using BWA-MEM (version 0.7.17).

Duplicate reads were marked and removed using Picard (version 3.1.1). Base quality score recalibration and variant calling were performed using GATK (version 4.5.0.0). Variant annotation was conducted with SnpEff (version 5.2), utilizing reference databases including dbSNP v156, 1000 Genomes Phase 3, ClinVar (July 2024 release), and ESP6500.

DNA Damage Response (DDR) Gene Panel Selection

For targeted analysis of DNA damage response (DDR) alterations, a curated gene panel comprising key DDR pathway genes was utilized. The panel included 52 genes involved in various DNA repair mechanisms, selected based on their well-established roles in genomic stability and cancer susceptibility.

The genes were categorized into the following DDR pathways: homologous recombination (HR), non-homologous end joining (NHEJ), mismatch repair (MMR), base excision repair (BER), nucleotide excision repair (NER), and translesion synthesis (TLS). Notable genes included BRCA1, BRCA2 (FANCD1), RAD51, and FANCA (HR); XRCC6 (ku70), XRCC5 (ku80) (NHEJ); MLH1, MSH2, PMS2 (MMR); OGG1, MUTYH (BER); ERCC family genes (ERCC1-8) (NER); and POLH, POLK (TLS). The full list of genes and their corresponding DDR pathways is presented in Table 1.

Variant Classification and Interpretation

Identified variants were classified following the guidelines of the American College of Medical Genetics and Genomics (ACMG), and assigned into one of five categories: pathogenic, likely pathogenic, variant of uncertain significance (VUS), likely benign, or benign.

The classification integrated multiple criteria, including population allele frequency data, computational predictive tools, functional evidence (when available), and data from curated databases such as ClinVar, COSMIC, and gnomAD. For this study, only

variants classified as pathogenic or likely pathogenic were included in further analyses, including correlation with clinical and demographic parameters.

Genotoxic Screens

To assess the potential impact of identified DDR gene alterations on chemotherapeutic sensitivity, we analyzed functional sensitivity scores based on data from The Durocher Lab Genotoxic Screens [15]. Genes were cross-referenced with published screens to evaluate predicted sensitivity to selected DNA-damaging agents.

Etoposide and cisplatin were chosen for this analysis because they are commonly used in medulloblastoma treatment regimens. Sensitivity profiles were visualized to highlight genes potentially contributing to altered responses to these agents in the context of DDR pathway deficiencies.

Statistical Analysis

Descriptive statistics were used to summarize clinical and demographic characteristics, as well as the distribution of DNA damage response (DDR) pathway mutations. Continuous variables, such as age at diagnosis, were compared between groups using the t-test. Associations between DDR pathway mutations and categorical clinical variables (e.g., tumor stage, metastasis status, survival outcome) were assessed using the chi-square test. All statistical analyses were performed using standard software (Jamovi, version 2.6.17), and a p-value < 0.05 was considered statistically significant.

Ethics approval and consent to participate

This study was approved by the Local Committee of Bioethics of the "University Medical Center" Corporate Fund, Kazakhstan (Protocol number: №8/2024/ПЭ, date: 03.09.2024). Written informed consent was obtained from all participants or their legal guardians prior to sample collection and data analysis. All procedures were conducted in accordance with the ethical standards of the institutional and national research committees, and with the Helsinki Declaration.

3. Results

A total of 42 pediatric patients with medulloblastoma were included in the study. The cohort consisted of 29 males (69.0%) and 13 females (31.0%). The mean age at diagnosis was 8.11 years (SD = 4.13), with a median age of 8 years. During the study period, 12 patients (28.6%) from this full cohort were reported deceased.

Detailed data on tumor stage and metastasis status were available for 34 patients. Among these, 2 patients (5.9%) had T1 tumors, 11 patients (32.5%) had T2, 5 patients (14.7%) had T3a, 12 patients (35.3%) had T3b, and 4 patients (11.8%) had T4 tumors. For metastasis status, 26 patients (76.5%) had no metastases (M0), 2 patients (5.9%) were classified as M2, and 6 patients (17.6%) as M3.

A total of 42 FFPE tumor samples were included in this retrospective analysis. On average, each sample yielded approximately 53 million reads (ranging from 41 to 58 million). After trimming, read lengths ranged from 100 to 135 base pairs. Most samples achieved a mean sequencing depth greater than 150×. The average percentage of target regions covered at ≥10x ranged from 95% to 99.8%. The average proportion of target regions covered at ≥30x was approximately 70%, varying between 30% and 90% depending on the sample. The average GC content across samples was around 55-60%, and the proportion of Q30 bases (quality score ≥30) was approximately 95%, indicating high overall sequencing quality.

Regarding variant detection, each sample contained approximately 70,000 to 76,000 single nucleotide polymorphisms (SNPs), with an average transition/transversion (Ts/Tv) ratio of 2.4-2.8. The proportion of known variants (based on dbSNP v156) ranged from 85% to 97%. Additionally, each sample contained approximately 9,000 to 13,000 insertions and deletions (INDELs).

Among the 42 pediatric medulloblastoma samples analyzed, pathogenic or likely pathogenic

mutations in DNA damage response (DDR) genes were detected in 30 cases (71.4%), while 12 cases (28.6%) showed no DDR gene alterations (wild type, WT).

The most frequently altered DDR pathway was homologous recombination (HR), with mutations identified in 19 cases (45.2%). Mismatch repair (MMR) pathway mutations were observed in 12 cases (28.6%), followed by nucleotide excision repair (NER) in 10 cases (23.8%). Non-homologous end joining (NHEJ) and translesion synthesis (TLS) pathways were each altered in one case (2.4%) (Figure 1B).

At the individual gene level, the most frequently mutated genes included ERCC6 (n = 7), SLX4, FANCM, and PMS1 (each n = 4), followed by PALB2, PMS2, and MSH6 (each n = 3). Mutations in other DDR genes, such as BRCA1, RAD50, FANCB, MSH2, and ERCC5, were less frequent, appearing in two cases each (Figure 1C).

Regarding mutation types, frameshift mutations were the most common, followed by nonsense and missense variants. Splicing mutations were less frequent (Figure 1A). Overall, these results highlight a substantial prevalence and diversity of DDR gene alterations, particularly in the HR and MMR pathways, among Kazakhstani children with medulloblastoma.

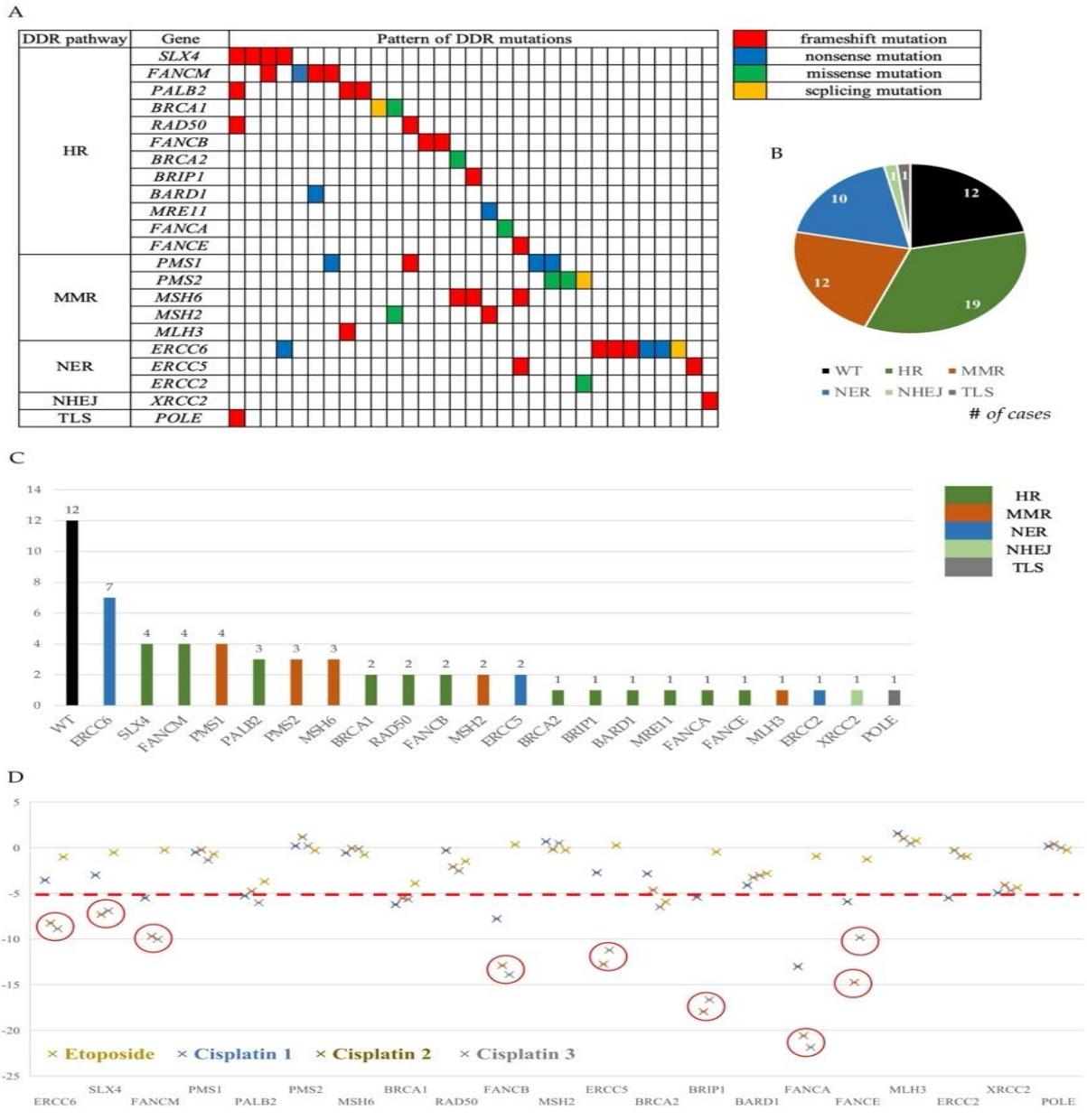

Figure 1 - Mutational landscape of DNA damage response (DDR) genes and genotoxic sensitivity profile in pediatric medulloblastoma samples

(A) Distribution and patterns of pathogenic and likely pathogenic DDR gene mutations across the cohort (n = 42). Color coding indicates mutation types: frameshift (red), nonsense (blue), missense (green), and splicing (yellow). Genes are grouped by DDR pathway: HR (homologous recombination), MMR (mismatch repair), NER (nucleotide excision repair), NHEJ (non-homologous end joining), and TLS (translesion synthesis). (B) Pie chart showing the distribution of DDR pathway alterations among cases. WT: no DDR gene mutations detected; HR: homologous recombination; MMR: mismatch repair; NER: nucleotide excision repair; NHEJ: non-homologous end joining; TLS: translesion synthesis. (C) Frequency of mutated DDR genes across samples. Color coding corresponds to DDR pathway assignment. (D) Sensitivity score analysis based on The Durocher Lab Genotoxic Screens dataset. Selected agents included etoposide and cisplatin, which are used in medulloblastoma treatment protocols. Genes associated with increased drug sensitivity are indicated with red circles, and the dashed red line represents the threshold of relative sensitivity.

A total of 46 pathogenic and likely pathogenic variants were identified across 24 DDR genes in the analyzed medulloblastoma samples (Table 2). The majority of variants were frameshift mutations (27/46, 58.7%), followed by nonsense mutations (8/46, 17.4%), missense mutations (7/46, 15.2%), and splicing mutations (4/46, 8.7%).

Table 1 - DNA Damage Response (DDR) Gene Panel

Gene	DDR Pathway	Gene	DDR Pathway	Gene	DDR Pathway
BARD1	HR	FANCF	HR	PMS1	MMR
BRCA1	HR	FANCG/XRCC	HR	PMS2	MMR
BRCA2/FANCD1	HR	FANCI	HR	POLD1	TLS
BRIP1/FANCJ	HR	FANCL/PHF9	HR	POLE	TLS
DDB1	NER	FANCM	HR	POLB	TLS
DDB2	NER	FANCN/PALB2	HR	POLH	TLS
ERCC1	NER	FANCP/SLX4	HR	POLK	TLS
ERCC2/XPD	NER	ku70/XRCC6	NHEJ	RAD50	HR
ERCC3/XPB	NER	ku80/XRCC5	NHEJ	RAD51	HR
ERCC4	NER	MLH1	MMR	RAD51C/FANCO	HR
ERCC5/BIVM	NER	MLH3	MMR	RAD51D	HR
ERCC6/CSB	NER	MRE11	HR	XPA	NER
ERCC8/CSA	NER	MSH2	MMR	XPC	NER
FANCA	HR	MSH3	MMR	XRCC2	NHEJ
FANCB	HR	MSH6	MMR	XRCC3	NHEJ
FANCC	HR	MUTYH	BER	XRCC4	NHEJ
FANCD2	HR	NBN	HR		
FANCE	HR	OGG1	BER		

HR – Homologous Recombination, NHEJ – Non-Homologous End Joining, MMR – Mismatch Repair, BER – Base Excision Repair, NER – Nucleotide Excision Repair, and TLS – Translesion Synthesis

Table 2 - Pathogenic and likely pathogenic DDR gene mutations identified in pediatric medulloblastoma samples

Gene	gDNA/cDNA	Amino Acid	Mutation
BARD1	c.2208T>G	p.Tyr736*	nonsense mutation
BRCA1	c.212+1G>A	-	splicing
BRCA1	c.5091T>G	p.Cys1697Trp	missense mutation
BRCA2	c.7826G>A	p.Gly2609Asp	missense mutation
BRIP1	c.585del	p.Asn196Thrfs*7	frameshift deletion
ERCC2	c.2150C>G	p.Ala717Gly	missense mutation
ERCC5	c.2751dup	p.Leu918Ilefs*12	frameshift duplication
ERCC6	c.1303G>T	p.Glu435*	nonsense mutation
ERCC6	c.2643del	p.Trp881*	nonsense mutation
ERCC6	c.2866_2867del	p.Leu956Valfs*15	frameshift deletion
ERCC6	c.3425del	p.Ser1142Leufs*10	frameshift deletion
ERCC6	c.3642del	p.Asp1214Glufs*13	frameshift deletion
ERCC6	c.3661C>T	p.Arg1221*	nonsense mutation
ERCC6	c.4062+1G>A	-	splicing
FANCA	c.2852G>A	p.Arg951Gln	missense mutation
FANCB	c.767_768del	p.Leu256Hisfs*18	frameshift deletion
FANCB	c.2178del	p.Met727Cysfs*14	frameshift deletion
FANCE	c.537_538insCC	p.Ser180Profs*117	frameshift insertion
FANCM	c.2201_2202dup	p.Glu735Leufs*26	frameshift duplication
FANCM	c.2663dup	p.Asn888Lysfs*10	frameshift duplication
FANCM	c.5180del	p.Leu1727*	nonsense mutation
MLH3	c.1755dup	p.Glu586Argfs*3	frameshift duplication
MRE11	c.324G>A	p.Trp108*	nonsense mutation
MSH2	c.2275G>A	p.Gly759Arg	missense mutation
MSH2	c.2377_2378del	p.Gln793Aspfs*5	frameshift deletion
MSH6	c.1530del	p.Arg511Glyfs*60	frameshift deletion
MSH6	c.1885del	p.Asp629Metfs*6	frameshift deletion
MSH6	c.3261del	p.Phe1088Serfs*2	frameshift deletion
PALB2	c.256del	p.Thr86Profs*91	frameshift deletion
PALB2	c.1868del	p.Lys623Serfs*5	frameshift deletion
PALB2	c.2092del	p.Leu698Phefs*11	frameshift deletion
PMS1	c.1258del	p.His420Ilefs*22	frameshift deletion
PMS1	c.1627G>T	p.Glu543*	nonsense mutation
PMS1	c.2654_2655del	p.Ser885*	frameshift deletion
PMS2	c.209A>G	p.Asp70Gly	missense mutation
PMS2	c.537+1G>A	-	splicing
POLE	c.4337_4338del	p.Val1446Glyfs*3	frameshift deletion
RAD50	c.2165del	p.Lys722Argfs*14	frameshift deletion
RAD50	c.2940_2943del	p.Asn981Lysfs*2	frameshift deletion

SLX4	c.1116_1117insT	p.Leu373Serfs*7	frameshift insertion
SLX4	c.1125del	p.Ala376Hisfs*21	frameshift deletion
SLX4	c.1621_1627del	p.Ala541Argfs*37	frameshift deletion
XRCC2	c.350dup	p.Leu117Phefs*6	frameshift duplication

Frameshift mutations were particularly prevalent in genes involved in homologous recombination (e.g., PALB2, FANCB, RAD50) and mismatch repair pathways (e.g., MSH6, PMS1), suggesting a potential impact on protein truncation and loss of function.

Overall, this mutation spectrum highlights the high degree of genetic heterogeneity within DDR pathways in pediatric medulloblastoma and underscores the prominent role of frameshift and nonsense variants in driving DDR deficiency in this cohort.

To explore potential functional implications of the identified DDR gene mutations on chemotherapeutic response, we analyzed genotoxic sensitivity scores based on The Durocher Lab Genotoxic Screens dataset. We specifically focused on etoposide and cisplatin, as these agents are commonly used in medulloblastoma treatment protocols.

Among the DDR genes harboring pathogenic or likely pathogenic mutations, several were associated with increased predicted sensitivity to cisplatin and/or etoposide. Notably, mutations in FANCA, FANCB, FANCE, FANCM, BRIP1, ERCC5, ERCC6, and SLX4 showed markedly negative sensitivity scores, indicating enhanced susceptibility to these DNA-damaging agents (Figure 1D, genes circled in red).

The overall pattern suggested that tumors with disruptions in homologous recombination (HR) and nucleotide excision repair (NER) pathways may exhibit heightened sensitivity to platinum-based agents. These findings provide a potential rationale for considering DDR mutational profiles in future risk stratification and treatment tailoring for pediatric medulloblastoma patients.

We further examined the association between DDR pathway mutational status and clinical features, including survival outcome (death), tumor stage, and metastasis status (Table 3).

Table 3 - Association between DDR pathway mutational status and clinical parameters in pediatric medulloblastoma cohort

DDR pathway mutational status	Death		Tumor stage		Metastasis	
	χ^2	p	χ^2	p	χ^2	p
HR	1.16	0.281	4.21	0.379	0.147	0.929
NER	0.01	0.909	3.44	0.487	5.35	0.069
MMR	1.41	0.235	3.69	0.449	1.26	0.532
Model 1	0.09	0.769	1.17	0.883	2.95	0.228

HR – Homologous Recombination, MMR – Mismatch Repair, NER – Nucleotide Excision, Model 1 - having at least one mutation in FANCA, FANCB, FANCE, FANCM, BRIP1, ERCC5, ERCC6, or SLX4

No statistically significant associations were found between mutations in homologous recombination (HR), nucleotide excision repair (NER), or mismatch repair (MMR) pathways and death (all $p > 0.2$), tumor stage (all $p > 0.3$), or metastasis status (all $p > 0.05$).

We analyzed a combined subgroup (Model 1) defined as having at least one mutation in FANCA, FANCB, FANCE, FANCM, BRIP1, ERCC5, ERCC6, or SLX4, which were genes associated with increased predicted sensitivity to cisplatin and/or etoposide.

Similar to the individual pathway analyses, no significant associations were observed between Model 1 status and death (p = 0.769), tumor stage (p = 0.883), or metastasis status (p = 0.228).

In addition to the categorical analyses, we also explored correlations between DDR variant burden and clinical parameters. We found that the total number of detected DDR variants was negatively correlated with tumor stage (r = -0.436, p = 0.019), suggesting that higher mutational burden in DDR genes may be associated with lower tumor stage at diagnosis.

Furthermore, the presence of variants in the translesion synthesis (TLS) pathway was positively correlated with metastasis status (r = 0.346, p = 0.045), indicating a potential link between TLS alterations and metastatic behavior in pediatric medulloblastoma.

4. Discussion

In this study, we comprehensively analyzed the mutational landscape of DNA damage response (DDR) pathway genes in a cohort of Kazakhstani children with medulloblastoma. We observed a high prevalence of pathogenic and likely pathogenic DDR gene mutations, detected in 71.4% of cases, with the most frequently affected pathways being homologous recombination (HR) and mismatch repair (MMR).

Frameshift and nonsense variants dominated the mutation spectrum, suggesting a strong potential for loss-of-function effects and impaired DNA repair capacity. Among individual genes, ERCC6, SLX4, FANCM, and PMS1 emerged as the most frequently mutated, highlighting possible key contributors to genomic instability in this cohort.

Through genotoxic sensitivity analysis, we found that several mutated genes (e.g., FANCA, FANCB, FANCE, FANCM, BRIP1, ERCC5, ERCC6, SLX4) were associated with increased predicted sensitivity to cisplatin and etoposide – agents commonly used in medulloblastoma treatment.

Although no statistically significant associations were observed between DDR pathway mutations and clinical parameters such as survival, tumor stage, or metastasis overall, we did identify notable correlations: the total number of DDR variants was negatively correlated with tumor stage, and the presence of translesion synthesis (TLS) variants was positively correlated with metastasis.

Together, these findings underscore the complex and heterogeneous nature of DDR gene alterations in pediatric medulloblastoma and suggest potential avenues for personalized therapeutic strategies in this patient population.

DDR Gene Mutation Landscape in Pediatric Medulloblastoma

Our study revealed a notably high prevalence of pathogenic and likely pathogenic DDR gene mutations (71.4%) among Kazakhstani children with medulloblastoma, with a predominance of alterations in the homologous recombination (HR) and mismatch repair (MMR) pathways. This rate is substantially higher than reported in large international cohorts, where germline DDR mutations have been observed in only 5-11% of patients [16].

Specifically, germline BRCA2 mutations occur in approximately 1% of medulloblastoma cases, often as truncating variants, and are sometimes associated with Fanconi anemia when biallelic [16]. Germline PALB2 mutations are even rarer (<1%), and BRCA1 alterations are uncommon both somatically (<6% in small series) and as germline drivers [17]. In our cohort, we identified recurrent HR pathway mutations, including in BRCA1, BRCA2, PALB2, FANCB, and FANCM, with a predominance of frameshift and nonsense variants.

Interestingly, other studies have reported HR gene mutations (such as FANCA and FANCM) only as isolated events, each affecting around 1% of patients [18]. Our higher frequency of these alterations may reflect regional or ethnic-specific genomic profiles or could be related to differences in patient selection or sequencing approaches.

For the MMR pathway, prior studies have consistently shown that somatic and germline MMR

mutations are exceedingly rare in medulloblastomas, with only isolated cases linked to constitutional MMR deficiency syndrome (CMMRD) presenting with ultra-hypermutation [16,17]. In contrast, we observed MMR gene alterations, including in MSH2, MSH6, and PMS1, suggesting a potentially higher burden of mismatch repair disruption in our cohort.

Regarding the nucleotide excision repair (NER) pathway, our data also diverged from previous reports. For example, a targeted analysis identified only a single ERCC2 variant (~1%) in prior studies, and ERCC6 mutations have generally not been highlighted as prominent [17,18]. However, ERCC6 emerged as one of the most frequently mutated genes in our series, further emphasizing possible regional or cohort-specific differences.

Finally, while overall DDR gene mutations are generally not recurrent at high frequency (>5%) in medulloblastoma outside of TP53, our findings suggest a distinct mutational signature in Kazakhstani pediatric patients, characterized by high DDR mutation rates and predominance of loss-of-function alterations. These results highlight the importance of investigating DDR pathway alterations in diverse populations to better understand tumor biology and to identify potential therapeutic vulnerabilities.

Impact of DDR Gene Mutations on Prognosis and Therapy Response

Alterations in DDR genes have significant implications for prognosis and therapy response in medulloblastoma patients. While no statistically significant associations between DDR mutations and survival, tumor stage, or metastasis were observed in our cohort overall, specific patterns suggest potential clinical relevance.

In other studies, TP53 mutations, particularly in the SHH subgroup, are strongly linked to poor outcomes and high chromosomal instability, defining a "very high-risk" group with 5-year survival as low as ~20% [17,18]. Similarly, biallelic BRCA2 (Fanconi anemia) mutations confer markedly poor prognosis due to complete homologous recombination deficiency and high treatment toxicity, whereas heterozygous BRCA2 or PALB2 mutations generally do not adversely impact survival [16]. Our data demonstrated multiple HR pathway alterations, including BRCA1, BRCA2, and PALB2, largely as heterozygous truncating mutations, which may have less prognostic impact but could signal underlying repair deficiencies and guide genetic counseling.

Mismatch repair (MMR) mutations are rare but clinically important, as MMR-deficient tumors are hypermutated and respond poorly to standard therapies while being potentially sensitive to immunotherapy [19]. Although we observed MMR gene variants in our cohort, their exact functional consequences require further investigation.

Importantly, germline DDR mutations have been associated with increased treatment-related toxicity in pediatric brain tumors, highlighting the need for close monitoring and potential therapy modification [18].

Lastly, DDR defects have been linked to aggressive disease features, such as metastasis at diagnosis, as reported for ATM and BRCA1 mutations in Taiwanese and other cohorts [17,20]. In our study, the positive correlation between TLS pathway variants and metastasis supports this notion, suggesting that certain DDR alterations might contribute to a more invasive phenotype.

Together, these findings underscore the emerging importance of DDR gene profiling in medulloblastoma for refining risk stratification, guiding treatment choices, including potential use of PARP inhibitors or immunotherapy, and improving supportive care planning.

Study limitations

This study has several important limitations. First, the retrospective design and single-institution setting may introduce selection bias and limit generalizability to broader pediatric populations. Second, although whole-exome sequencing was performed, the analysis focused specifically on a predefined DDR gene panel, potentially missing other relevant alterations or broader genomic context (such as copy number variations or structural rearrangements). Third, functional validation of identified variants was not conducted; therefore, the actual biological impact of some mutations, particularly missense and splicing variants,

remains uncertain. Additionally, incomplete clinical data for a subset of patients restricted some correlation analyses. Finally, while our cohort is relatively large for a single-center pediatric study, larger multi-institutional studies are needed to confirm these findings and strengthen statistical power.

Future Perspective

Moving forward, comprehensive genomic profiling, including integration of whole-genome sequencing and methylation data, could provide deeper insights into the molecular landscape and epigenetic regulation of medulloblastoma in different populations. Functional studies to clarify the pathogenicity of specific DDR variants, particularly rare or novel mutations, will be critical. Moreover, prospective trials incorporating DDR mutation status into risk stratification and treatment planning are warranted. Investigating the potential role of targeted agents, such as PARP inhibitors for HR-deficient tumors or immune checkpoint inhibitors for hypermutated MMR-deficient cases, represents a promising area for future research. Finally, incorporating germline DDR mutation screening into routine clinical practice may help guide personalized therapy choices and inform family counseling.

5. Conclusion

In summary, our study provides the first comprehensive analysis of DNA damage response gene mutations in Kazakhstani children with medulloblastoma, revealing a high prevalence of DDR alterations, particularly in homologous recombination and mismatch repair pathways. The predominance of truncating mutations underscores the potential role of DDR deficiency in tumorigenesis and therapy response. While no significant associations with clinical outcomes were found overall, specific correlations, such as the link between TLS variants and metastasis, suggest a possible contribution to tumor aggressiveness. These findings highlight the importance of integrating DDR profiling into medulloblastoma research and clinical care, paving the way for future precision medicine approaches aimed at improving outcomes in this vulnerable population.

Conflicts of Interest. The authors declare no conflicts of interest.

Acknowledgments. We sincerely thank all the participants and their legal guardians for their invaluable contribution to this study.

Funding. This research has been funded by the Committee of Science of the Ministry of Science and Higher Education of the Republic of Kazakhstan (grant title: Study of molecular genetic features and monitoring of the effectiveness of medulloblastoma therapy in children: a step towards personalized therapy, grant No. AP23490016).

Author Contributions. Conceptualization, M.B., A.Z., R.N., and A.B.; methodology, M.B., A.Z., R.N., and A.B.; validation, M.S., A.A., B.I., Z.Z., and B.Z.; formal analysis, A.B.; investigation, A.Z., M.S., A.A., R.N., B.I., Z.Z., O.G., B.Z., and S.I.; resources, M.B., B.I., and B.Z.; data curation, A.Z., M.S., A.A., R.N., B.I., Z.Z., O.G., B.Z., and S.I.; writing – original draft preparation, A.Z., M.S., A.A., and A.B.; writing – review and editing, M.B., R.N., B.I., Z.Z., O.G., B.Z., and S.I.; visualization, A.B.; supervision, M.B.; project administration, M.B., R.N., B.I., and O.G.; funding acquisition, M.B. All authors have read and agreed to the published version of the manuscript.

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Қазақстандық медуллобластомасы бар балалардағы ДНҚ зақымдануына жауап беру жолдарының мутациялық ландшафты

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Түйіндеме

Кіріспе. Медуллобластома (MB) – балалардағы ең жиі кездесетін қатерлі ми ісігі, және ДНҚ зақымына жауап беру (DDR) гендеріндегі өзгерістер ісіктің дамуына, емге жауапқа және болжамға әсер етуі мүмкін. Алайда, Орталық Азиядағы педиатриялық популяцияда DDR мутацияларының ландшафты әлі зерттелмеген.

Әдістері. 2015–2024 жылдар аралығында Қазақстандағы «University Medical Center» Корпоративтік Қорынан алынған 42 балалар MB үлгісіне ретроспективті талдау жүргізілді. Формалинмен бекітілген, парафинделген тіндерден (FFPE) бөлінген ДНҚ-ға толық экзомды секвенирлеу жасалып, DDR жолдарының 52 гені мақсатты түрде талданды. Варианттар ACMG нұсқауларына сәйкес классификацияланды және клиникалық деректермен байланысы бағаланды.

Нәтижесі. 71,4% жағдайларда патогенді немесе ықтимал патогенді DDR ген мутациялары анықталды, көбінесе гомологтық рекомбинация (HR) және қате сәйкестікті түзету (MMR) жолдарының өзгерістері басым болды. Ең жиі кездесетін мутациялар – фреймшифт және нонсенс түрлері. Жиі мутацияланған гендерге ERCC6, SLX4, FANCM және PMS1 кірді. Функционалдық сезімталдық талдауы HR және нуклеотид эксцизиялық репарация (NER) жолдарының мутациялары цисплатин мен этопозидке жоғары сезімталдық беруі мүмкін екенін көрсетті. Жалпы алғанда, DDR статусы мен тірі қалу немесе ісіктің сатысы арасында айтарлықтай

байланыс табылмады; алайда, DDR варианттарының жалпы саны ісік сатысымен кері корреляция көрсетті (r = –0,436, p = 0,019), ал транслезиялық синтез (TLS) жолының варианттары метастазбен оң корреляция көрсетті (r = 0,346, p = 0,045).

Қорытынды. Бұл зерттеу балалар МБ науқастарында DDR ген мутацияларының жоғары жиілігін көрсетіп, DDR өзгерістерінің қауіп стратификациясы мен жекелендірілген емдік стратегиялардағы ықтимал клиникалық маңыздылығын атап өтті. Нәтижелер DDR профилин болашақ МБ зерттеулеріне және емдеу жоспарлауға енгізуді қолдайды.

Түйін сөздер: медуллобластома, ДНҚ зақымына жауап беру, балалардың ми ісігі, мутациялар, дербестендірілген медицина.

Мутационный ландшафт путей ответа на повреждение ДНК у казахстанских детей с медуллобластомой

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Резюме

Введение. Медуллобластома (МБ) является наиболее распространённой злокачественной опухолью головного мозга у детей, и изменения в генах ответа на повреждение ДНК (DDR) могут влиять на опухолевый процесс, чувствительность к лечению и прогноз. Однако ландшафт мутаций DDR у детей Центральной Азии до сих пор не был изучен.

Методы. Мы провели ретроспективный анализ 42 образцов МБ у детей, собранных в Корпоративном Фонде «University Medical Center» (Казахстан) в период с 2015 по 2024 год. ДНК, выделенная из опухолевых тканей, фиксированных в формалине и залитых в парафин (FFPE), была подвергнута полноэкзомному секвенированию с целевым анализом 52 генов пути DDR. Варианты классифицировались в соответствии с руководствами ACMG, и проводилась оценка их корреляции с клиническими данными.

Результаты. Патогенные или вероятно патогенные мутации генов DDR были выявлены в 71,4% случаев, при этом преобладали изменения в путях гомологичной рекомбинации (HR) и исправления ошибочной репарации (MMR). Наиболее частыми типами мутаций были сдвиг рамки считывания (frameshift) и нонсенс-мутации. Чаще всего мутации наблюдались в генах ERCC6, SLX4, FANCM и PMS1. Функциональный анализ чувствительности показал, что мутации путей HR и эксцизионной репарации нуклеотидов (NER) могут способствовать повышенной чувствительности к цисплатину и этопозиду. Общих значимых ассоциаций между статусом DDR и выживаемостью или стадией опухоли выявлено не было; однако общее количество вариантов DDR отрицательно коррелировало со стадией опухоли ($r = -0,436$, $p = 0,019$), а варианты пути транслезионного синтеза (TLS) положительно коррелировали с наличием метастазов ($r = 0,346$, $p = 0,045$).

Выводы. Данное исследование демонстрирует высокую распространённость мутаций генов DDR среди детей с МБ, подчёркивая потенциальную клиническую значимость этих изменений для стратификации риска и разработки персонализированных терапевтических стратегий. Полученные данные поддерживают необходимость интеграции профилирования DDR в будущие исследования и планирование лечения МБ.

Ключевые слова: медуллобластома, ответ на повреждение ДНК, опухоль головного мозга у детей, мутации, прецизионная медицина.