

## REVIEW ARTICLE

# Oncogenic role of *HERC2* in familial glioma development: A review

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## Abstract

Familial gliomas are rare primary brain tumors, accounting for around 5% of all glioma cases, and carry a strong familial predisposition, although their genetic basis remains incompletely understood. A recent 2023 Stanford study discovered that genome-wide sequencing has identified deleterious variants in HECT and RCC1-like domain-containing protein 2 (*HERC2*), the most significantly enriched gene in familial glioma cohorts. HECT and RLD domain containing E3 ubiquitin protein ligase 2 (*HERC2*), a large (~528 kDa) multifunctional E3 ubiquitin ligase, modulates DNA damage responses by catalyzing ubiquitin signaling cascades, facilitating the recruitment of repair proteins (breast cancer 1, p53-binding protein 1) through the ring finger protein 8/ubiquitin conjugating enzyme E2 13 complex, regulating p53 tetramerization through neutralized E3 ubiquitin protein ligase 4/E6-associated protein complexes, and controlling intra-S-phase checkpoint activation through the ubiquitin-specific peptidase 20-Claspins-checkpoint kinase 1 axis. Structurally, *HERC2* comprises RCC1-like domains for chromatin engagement, a mind bomb/*HERC2* domain for E2 interactions, a CPH domain implicated in p53 stabilization, a ZZ-type zinc finger, a DOC scaffold region, and a catalytic C-terminal HECT domain. Familial glioma-associated *HERC2* mutations include missense variants and truncating loss-of-function alleles that impair ubiquitin-mediated coordination of normal protein degradation, induce *TP53* dysfunction, and promote genomic instability. These findings highlight *HERC2*'s potential as a diagnostic biomarker and therapeutic target. Future studies are needed to determine the penetrance of *HERC2* variants and assess their prognostic and predictive value in clinical practice.

**Keywords:** Brain tumor; HECT and RCC1-like domain-containing protein 2; Familial glioma; Ubiquitin signaling; *TP53*; Genomic instability

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## 1. Introduction

Gliomas are the most prevalent primary malignant brain tumors in adults. These tumors arise from glial or precursor cells and are categorized into adult- and pediatric-type (low/high grade), circumscribed astrocytic gliomas, glioneuronal and neural tumors, ependymal tumors, and choroid plexus tumors.<sup>1</sup> Gliomas constitute approximately 30% of the central nervous system tumors, and account for the majority (81%) of malignant brain tumors among young adults.<sup>2</sup> Despite accounting for a significant proportion of malignant central nervous system tumors, gliomas are still considered rare, with an incidence rate of 6/100,000 individuals in the United States. It is also associated with a poor prognosis, with a median survival of 14 months.<sup>2,3</sup> Among glioma cases, approximately 5% are identified as familial.<sup>4,5</sup> Familial glioma is defined as the occurrence of gliomas in two or more first-degree relatives, often presenting at younger ages. Patients with first-degree relatives with gliomas have a two-fold increased risk of developing brain tumors.<sup>6</sup> The male-to-female ratio of familial glioma is 1.15 to 1, suggesting a slightly higher incidence in males than in females.<sup>7</sup> Despite this information and improved management over the past decades, its etiology and genetic basis remain obscure.

The classification of gliomas was originally based on their histological features; however, this approach resulted in high intra- and inter-observer pathologist variability and a poor prognosis.<sup>8</sup> The discovery of various molecular markers involved in glioma pathogenesis has provided a more accurate stratification of the condition as compared to histopathology alone. Isocitrate dehydrogenase (*IDH*)1 and *IDH*2 mutations, as well as concurrent loss of both 1p and 19q chromosome arms (1p/19q co-deletion), were used to subdivide gliomas into astrocytoma, oligodendroglioma, or glioblastoma. According to the 2021 World Health Organization's classification of central nervous system tumors, astrocytomas are characterized by the presence of *IDH* mutations without 1p/19q co-deletion, whereas oligodendrogliomas are defined by the presence of both an *IDH* mutation and 1p/19q co-deletion.<sup>9</sup> Conversely, glioblastomas are now defined as *IDH*-wildtype tumors and are no longer classified as *IDH*-mutant. *IDH*-mutant gliomas have decreased production of nicotinamide adenine dinucleotide phosphate and elevated 2-hydroxyglutarate levels, leading to DNA hypermethylation and increased histone methylation.<sup>10</sup> Interestingly, localized immune responses and glioma-induced epilepsy are seen in patients with increased 2-hydroxyglutarate.<sup>11</sup> Aside from these two important molecular markers, other biomarkers have been identified to classify further gliomas, such as *ATRX*, *TP53*, *NOTCH1*,

*FUBP1*, *MYB*, *H3K27*, and *CDKN2* gene mutations. Homozygous deletions in the *CDKN2A/CDKN2B* genes have been associated with a worse prognosis in *IDH*-mutated astrocytoma.<sup>12</sup>

Genetic predisposition plays a significant role in the development of familial glioma. Various hereditary cancers have been associated with increased risk of familial glioma, such as Lynch syndrome (mismatch repair gene mutations, such as *MLH1*, *MSH2*, *MSH6*, and *PMS2*),<sup>13</sup> neurofibromatosis types 1 and 2 (*NF1* and *NF2* mutations),<sup>14</sup> Li-Fraumeni syndrome (*TP53* mutations),<sup>15</sup> and melanoma-neural system tumor syndrome (*CDKN2A* mutations).<sup>16</sup> However, these syndromes only represent a small fraction of familial glioma cases, indicating the involvement of other genetic factors. Identification of several common low-penetrance variants was also conducted to elucidate familial glioma risk. Notable loci include 5p15.33 (*TERT*), 8q24.21 (*CCDC26*), 9p21.3 (*CDKN2B*), 11q23.3 (*PHLDB1*), 20q13.33 (*RTEL1*), and 7p11.2 (*EGFR*).<sup>17</sup> These findings suggest the polygenic model of inheritance for familial glioma and the contribution of multiple low-risk alleles in disease susceptibility. Aside from these, genome-wide sequencing was also employed to identify previously undescribed cancer predisposition genes. In a study by Choi *et al.*,<sup>18</sup> rare and highly deleterious single-nucleotide variants were found across seven genes in cohorts of patients with a history of familial glioma.<sup>18</sup> Specifically, HECT and RCC1-like domain-containing protein 2 (*HERC2*) was found to have the highest enrichment with deleterious variants compared to an ancestry-matched control group using a gene-based rare variant burden analysis. This enrichment reached experiment-wide significance following multiple-testing correction based on minor allele frequency, loss-of-function, and deleteriousness, suggesting its strong potential role in familial glioma predisposition. Furthermore, six mutations in the *HERC2* gene were found: Five rare coding variants that are considered to be highly deleterious single-nucleotide variants and one internal copy gain variant.<sup>18</sup> Importantly, the study controlled for population stratification by using ancestry-matched controls and performing principal component analysis on genome-wide single-nucleotide polymorphism data to minimize confounding due to residual population background. Despite this information, the exact role of *HERC2* mutations in familial glioma is still unclear.

## 2. The biology of HERC2

*HERC2* is a large (~528 kDa; 4,834 amino acid protein) and multifunctional E3 ubiquitin ligase responsible for various biological roles in genome integrity, DNA repair, and cellular homeostasis.<sup>19</sup> It has a highly complex structure,

comprising six major parts (Figure 1). HERC2 contains three RCC1-like domains (RLD1 – 3) located toward the N-terminal region, which regulate chromatin binding dynamics and are hypothesized to facilitate protein-protein interactions.<sup>20</sup> The cytochrome b5-like domain remains poorly understood, but it may contribute to structural integrity or serve as a scaffold for oxidation-reduction interactions.<sup>21</sup> HERC2 also harbors a mind bomb/HERC2 (M-H) domain, which shares homology with other HECT-type E3 ligases that are crucial for interactions with E2 conjugating enzymes.<sup>22</sup> The CPH domain, shared with Cullin 7 and p53-associated, parkin-like cytoplasmic protein, plays a role in stabilizing multi-protein complexes and may be essential for modulating p53 activity and DNA repair pathways.<sup>23</sup> Embedded within the central region is a ZZ-type zinc finger, a domain often implicated in substrate recognition and ubiquitin chain specificity.<sup>24</sup> The DOC domain, classically associated with Cullin-RING ligases, is responsible for molecular scaffolding or ubiquitin complex assembly.<sup>25</sup> Finally, the C-terminal HECT domain is the catalytic center of the protein, where ubiquitin is transferred from E2 enzymes to specific substrates through a thioester intermediate – a hallmark of the HECT E3 ligase family.<sup>26</sup> HERC2 is structurally diverse and modular in composition, allowing it to act as both a catalytic and scaffolding hub in critical cellular pathways, particularly those in DNA damage responses (DDR), regulation, and protein homeostasis.<sup>27</sup>

HERC2 plays a role in the DDR signaling pathway through its E3 ubiquitin ligase activity.<sup>22</sup> It catalyzes the transfer of ubiquitin moieties to specific target proteins, which are responsible for maintaining genomic integrity. In response to DNA double-strand breaks, HERC2 orchestrates a ubiquitin signaling cascade by facilitating the assembly of the ring finger protein 8 (RNF8)/ubiquitin conjugating enzyme E2 13 (UBC13) complex, a crucial process in recruiting downstream repair proteins, such as breast cancer 1 (BRCA1) and p53-binding protein 1 (53BP1), to the site of damage.<sup>28</sup> HERC2 is also recruited to the sites of DNA lesions through ataxia telangiectasia mutated (ATM)-dependent signaling and small ubiquitin-like modifier post-translational modification, facilitating stabilization and localization of RNF8 through small ubiquitin-like modifier-interacting zinc finger motif and thus, amplifying ubiquitin signaling on chromatin.<sup>29</sup> Furthermore, HERC2 selectively recruits ATM and ataxia-

telangiectasia and Rad3-related protein (ATR) kinases to modulate p53 stability downstream throughout the DDR cycle, regulating p53 transcriptional activity and influencing cell cycle arrest following genetic stress.<sup>24</sup> Moreover, HERC2 functions as a dual-acting ligase and platform protein, integrating ubiquitin-dependent signaling with chromatin remodeling and checkpoint activation to ensure efficient DNA repair and cellular recovery from genotoxic insults.

### 3. Role of HERC2 in genomic stability and cell cycle control

HERC2 is a multifunctional E3 ubiquitin ligase with two characteristic domains in its sequence, the HECT ubiquitin-ligase domain and RLDs. Among the six human HERC proteins, the large HERCs (HERC1/2) differ from the small HERC3–6 family members by containing three RLDs along with several additional motifs (M-H, CPH, ZZ zinc-finger, cytochrome-b5-like, and DOC/APC10 regions).<sup>22,30,31</sup> The said structure creates an extensive docking surface which allows HERC2 to couple chromatin recognition (via RLDs) to ubiquitin signaling (via the HECT active site), thereby positioning it to regulate complex, multi-protein interactions that maintain genome integrity through its multifaceted roles in DNA repair and cell cycle regulation. It coordinates multiple aspects of the DDR, cell cycle checkpoint control, and replication licensing, thereby ensuring proper cell proliferation and genome integrity.<sup>23</sup>

#### 3.1. HERC2 as a coordinator of cell cycle checkpoint regulation

HERC2 regulates the cell cycle by integrating DNA damage signals into checkpoint regulation mechanisms. It affects key transition points in the cell cycle, particularly the G1/S and G2/M phases, by adjusting the activity of important checkpoint proteins and factors involved in DNA replication. Unlike well-known DNA repair genes, such as *TP53*, *ATRX*, or *IDH1*, which primarily influence genomic stability through direct DNA repair or metabolic signaling, *HERC2* acts as an upstream regulator, controlling protein-protein interactions and ubiquitin-mediated degradation to maintain cell cycle fidelity.<sup>24</sup>

A central function of HERC2 in cell cycle control is its role in activating p53, a crucial tumor suppressor protein. It forms a ternary complex with neutralized E3



**Figure 1.** HECT and RCC1-like domain-containing protein 2 (HERC2) structure. It has three RCC1-like domains (RLD1–3), a cytochrome b5-like region (Cyt b5), the mind-bomb/HERC2 (M-H) domain, a CPH domain, a ZZ-type zinc finger, a DOC domain, and the homologous to E6-AP carboxyl terminus (HECT) domain. Created in BioRender.com. Relacion, P. (2025). <https://BioRender.com/zf7syvs>.

ubiquitin protein ligase 4 (NEURL4) and the E3 ligase E6-associated protein to promote the tetramerization of p53, a conformation necessary for its full transcriptional activity.<sup>23</sup> Once activated, p53 initiates transcription of critical checkpoint genes, such as *CDKN1A* (p21), *GADD45*, and *BAX*, and pro-apoptotic effectors, enforcing arrest at the G1/S or G2/M checkpoints depending on the phase of damage detection.<sup>32</sup> This checkpoint enforcement temporarily prevents cells with DNA defects from entering S phase or mitosis, thereby preserving genomic integrity. Interestingly, loss of HERC2 function can impair p53 transcriptional activity even when the *TP53* gene is not mutated. Such impairment can mimic p53 loss and potentially contribute to gliomagenesis in a *TP53*-independent manner.<sup>23</sup>

In addition to its role with p53, HERC2 regulates the stability and function of key DNA replication licensing factors, including chromatin licensing and DNA replication factor 1 and the origin recognition complex. Under conditions of replication stress or DNA damage, HERC2 ubiquitinates chromatin licensing and DNA replication factor 1, marking it for degradation by the proteasome. This prevents improper re-replication of DNA, helping maintain genome stability.<sup>22,33</sup> This activity is part of HERC2's wider role in coordinating the DDR, where it also supports the recruitment and stabilization of repair proteins, such as RNF8 and BRCA1, at sites of double-strand breaks.<sup>22,34</sup>

In addition, HERC2 plays a role in regulating the intra-S-phase checkpoint by modulating the Claspin-checkpoint kinase 1 (CHK1) signaling axis through its control of ubiquitin-specific peptidase 20 (USP20), a deubiquitinase that stabilizes Claspin. Under basal conditions, HERC2 promotes the degradation of USP20, which keeps Claspin levels low and limits CHK1 activation.<sup>35</sup> This allows DNA replication to proceed without unnecessary interruption. However, during replication stress, such as when single-stranded DNA accumulates, ATR, a central kinase in the response to replication stress, becomes activated. ATR phosphorylates USP20, disrupting its interaction with HERC2. As a result, USP20 is stabilized, leading to the accumulation of Claspin and subsequent activation of CHK1. Activated CHK1 then slows or halts DNA replication, providing the cell with time to resolve replication-associated DNA damage. Through this mechanism, HERC2 acts as a regulatory switch, maintaining low checkpoint activity during normal replication but allowing for rapid activation of the ATR-CHK1 pathway under stress. This ensures both efficient DNA synthesis and timely responses to replication stress, preserving genome stability.<sup>36</sup>

### 3.2. HERC2 as a genome custodian: The role of ubiquitin ligase in modulating the DNA-damage response

HERC2 safeguards genome integrity through multiple mechanisms, with its most well-characterized function being the regulation of the double-strand break response in DDR. As a HECT-type E3 ubiquitin ligase, HERC2 facilitates the recruitment and assembly of the RNF8-UBC13 ubiquitin signaling complex at double-strand break sites. This process leads to the ubiquitination of histone H2A and H2AX at chromatin flanking the damage, creating a platform for the recruitment of DNA repair proteins, such as 53BP1 and BRCA1. These proteins are essential for the execution of non-homologous end joining and homologous recombination, respectively, enabling efficient and accurate DNA repair.<sup>22,29</sup>

Apart from initiating DDR signaling, HERC2 also helps terminate repair processes and reset chromatin structure by regulating deubiquitinases, such as ubiquitin-specific peptidase 16. This ensures that repair sites are resolved properly and chromatin returns to its normal state.<sup>37</sup> In addition, HERC2 supports the cell's ability to cope with replication stress by coordinating the activity of the Bloom syndrome protein and Werner syndrome adenosine triphosphate-dependent helicase with the single-stranded DNA-binding protein replication protein A, promoting replication fork restart and stability. Loss of HERC2 disrupts the integrity of these complexes, resulting in fork collapse and accumulation of under-replicated DNA.<sup>38</sup>

Furthermore, HERC2 modulates the nucleotide excision repair pathway by stabilizing the xeroderma pigmentosum group A protein through ATR-mediated phosphorylation, aiding in the removal of ultraviolet-induced lesions.<sup>39</sup> Collectively, these functions emphasize HERC2's role as a custodian of genomic stability by coordinating the addition, recognition, and removal of ubiquitin marks at sites of DNA damage. It also helps align helicase and single-strand DNA-binding activities at stalled replication forks, ensuring the timely resolution of damage signaling. Impaired HERC2 function compromises multiple DNA repair pathways, increases replication stress, and promotes chromosomal instability, all of which are hallmarks of oncogenic transformation, including gliomagenesis.<sup>23</sup>

### 3.3. Role of HERC2 in DDR signaling and chromatin-based repair

In contrast to other glioma-associated genes, *HERC2* does not act directly on DNA or chromatin; it functions as an upstream integrator of checkpoint signaling. *TP53*, one of the most frequently mutated genes in glioma, directly controls cell cycle arrest and apoptosis following DNA

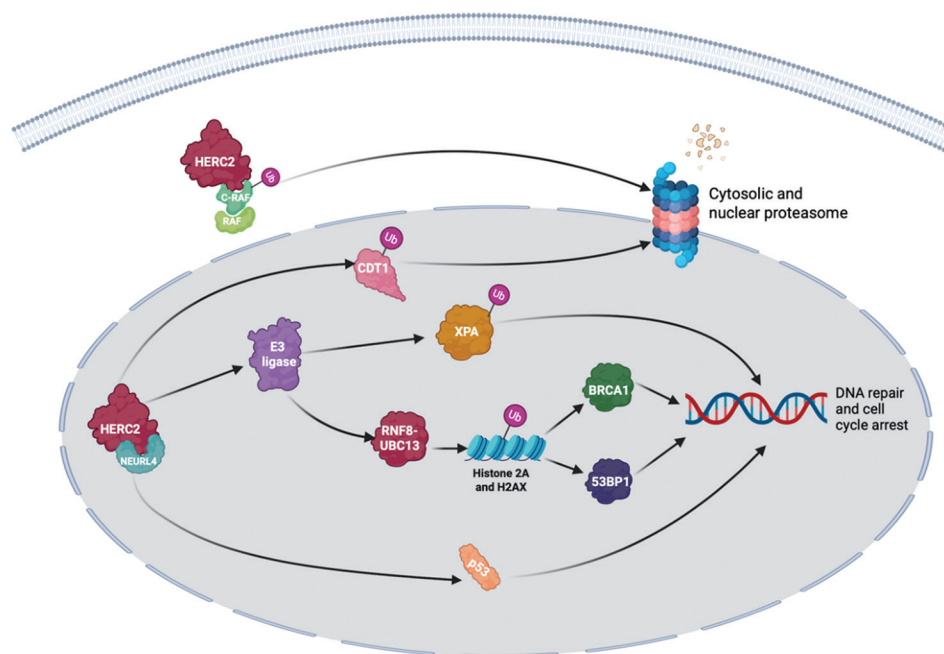


damage. When mutated, it leads to unregulated cell cycle progression due to loss of transcriptional control. As discussed previously, *HERC2* acts upstream as a modulator of p53 activation by promoting p53 tetramerization. Thus, its loss can impair p53 activity even in the absence of *TP53* mutations.<sup>40</sup> *ATRX* is a chromatin remodeler that protects telomeres and stabilizes replication forks, especially in the alternative lengthening of telomeres pathway seen in lower-grade gliomas.<sup>41</sup> Like *ATRX*, *HERC2* also aids in chromatin-based DNA repair processes, though it primarily does so by ubiquitylating histones and recruiting repair factors rather than remodeling nucleosomes. *IDH1*, frequently mutated in diffuse gliomas, promotes an oncometabolic state through the production of 2-hydroxyglutarate, which alters the cell's epigenetic landscape and indirectly disrupts homologous recombination.<sup>42</sup> While *IDH1* mutations lead to indirect defects in DNA repair through epigenetic dysregulation, *HERC2* directly orchestrates the recruitment and function of homologous recombination components at DNA breaks. Thus, *HERC2* serves as a connection that links DNA damage sensing to the enforcement of cell-cycle arrest through targeted ubiquitination. Although its functions overlap with those of *TP53*, *ATRX*, and *IDH1*, *HERC2* plays a distinct and complementary role in genome surveillance (Figure 2).

*HERC2* is an essential genome guardian that plays a role in DNA repair, cell cycle checkpoint control, and tumor suppression. Through its E3 ligase activity and coordination of repair complex assembly, *HERC2* ensures that damaged DNA is properly recognized and repaired before cell division. It interacts with a wide range of proteins to regulate critical cellular processes involved in the DDR, chromatin remodeling, and cell cycle control. Loss or dysfunction of *HERC2*, similar to that of *TP53*, *ATRX*, or *IDH1*, compromises genomic integrity and may drive gliomagenesis by allowing the accumulation of mutations and chromosomal instability. Understanding *HERC2*'s integrated role alongside other glioma-relevant genes opens new avenues for therapeutic strategies targeting DNA repair vulnerabilities in gliomas. A summary of the key protein interactions of *HERC2* and its activity is presented in Table 1.

#### 4. *HERC2* mutations in familial glioma and their tumorigenic implications

Gliomas are a diverse group of tumors originating from glial cells in the brain and spinal cord, representing the most common primary brain tumor within the central nervous system.<sup>43</sup> In 2023, the Stanford Medicine-led study identified over 50 genes potentially linked to familial



**Figure 2.** HECT and RCC1-like domain-containing protein 2 (*HERC2*) role in DNA repair and cell cycle control. *HERC2* regulates DNA replication licensing through chromatin licensing and DNA replication factor 1 (CDT1) ubiquitination (Ub), and modulates DNA repair through ubiquitination of xeroderma pigmentosum group A (XPA) and recruitment of the ring finger protein 8 (RNF8)-ubiquitin conjugating enzyme E2 13 (UBC13) complex at double-strand breaks. It also enhances p53-mediated stress responses by promoting p53 tetramerization and nuclear retention through interaction with neuralized-like protein 4 (NEURL4). Created in BioRender. Relacion, P. (2025). <https://BioRender.com/f7qm3n9>.

**Table 1. Summary of the key protein interactions of HECT and RCC1-like domain-containing protein 2 in various cellular processes**

Type	Protein	Mechanism	References
DNA damage response and repair	RNF8	HERC2 physically interacts with RNF8 and stabilizes the RNF8-UBC13 complex at sites of double-strand breaks. Consequently, HERC2 promotes K63-linked polyubiquitination of histones and recruitment of DNA repair factors.	24,42
	XPA	HERC2 targets XPA for ubiquitination, regulating nucleotide excision repair activity and ensuring DNA repair fidelity.	43
	BRCA1 and 53BP1	Recruitment of these proteins to the DNA damage foci is indirectly dependent on HERC2-mediated RNF8 ubiquitin signaling.	22
p53 pathway regulation	p53	HERC2 modulates p53 activity by promoting p53 tetramerization and nuclear retention. Hence, HERC2 influences p53-dependent transcriptional responses to genotoxic stress.	44
	NEURL4	HERC2 forms a complex with NEURL4 and p53 to promote oligomerization and enhance its tumor suppressor functions.	45
Chromatin and cell cycle regulation	USP16	HERC2 regulates USP16 stability through ubiquitination and, in turn, controls chromatin de-ubiquitination and histone H2A signaling.	36
	BLM and WRN	HERC2 has been shown to regulate the stability of these RecQ helicases, both of which are critical for DNA replication and repair of stalled replication forks	37

Abbreviations: 53BP1: p53-binding protein 1; BLM: Bloom syndrome protein; BRCA1: Breast cancer 1; HERC2: HECT and RCC1-like domain-containing protein 2; NEURL4: Neuralized E3 ubiquitin protein ligase 4; RNF8: Ring finger protein 8; UBC13: Ubiquitin conjugating enzyme E2 13; USP16: Ubiquitin-specific peptidase 16; WRN: Werner adenosine triphosphate-dependent helicase; XPA: Xeroderma pigmentosum group A.

glioma, with *HERC2* among the mutations found in affected families.<sup>44</sup> Although the article does not elaborate on *HERC2* specifically, its inclusion suggests a possible role in inherited susceptibility to glioma that warrants further investigation, especially since the *HERC2* protein was not previously associated with cancer. However, as of current evidence, the identified *HERC2* variants have not been conclusively shown to co-segregate with glioma within families, and there is limited to no published family-based co-segregation data assessing the penetrance or variable expressivity of these variants in glioma, as it needs co-segregation analysis within pedigrees. Without such data, causal interpretations remain incomplete and speculative.

Moreover, *HERC2* mutations appear to be rare or undocumented in sporadic glioma cases. A study by Kim *et al.*<sup>45</sup> conducted a next-generation sequencing analysis of astrocytomas, oligodendrogliomas, and glioblastomas ( $n \approx 147$  tumors;  $\sim 301$  variants across 68 genes), showing no significant mutation frequency in *HERC2*. Instead, commonly mutated genes in these tumors include *TP53* (31%), *IDH1* (24%), *TERT* promoter (23%), *PIK3CA*, *EGFR*, *NF1*, *PTEN*, *ATRX*, *RB1*, *BRAF*, *CIC*, and *PIK3R1*. Due to the absence of *HERC2* alterations in these cohorts, no clinical or prognostic associations, such as treatment response, survival outcomes, or tumor grading, have been reported in the context of sporadic glioma.<sup>45</sup>

As previously mentioned, *HERC2* is an E3 ubiquitin ligase that plays a critical role in essential cellular functions, including DNA repair, cell cycle control, and the regulation

of p53-mediated tumor suppression.<sup>46</sup> Emerging evidence suggests that mutations in *HERC2*, such as missense, truncating, and loss-of-function variants, are increasingly linked to gliomagenesis development and progression.<sup>47</sup>

Domain-level analysis of the identified familial glioma-associated *HERC2* variants reveals clustering on *HERC2* domains. Mutations in the HECT domain are expected to disrupt *HERC2*'s E3 ligase function, impairing the ubiquitin transfer required for K63-linked polyubiquitination of histones and recruitment of homologous DNA repair factors, such as BRCA1 and 53BP1.<sup>24</sup> Variants in the CPH or ZZ domains of *HERC2* may compromise p53 transcriptional activity responding to genotoxic stress, which plays a role in p53 stabilization through NEURL4-mediated tetramerization.<sup>40</sup> Potential alterations in the DOC domain may further impair assembly with checkpoint mediators and thereby disrupt cell cycle regulation.<sup>48</sup> These domain-specific mutations in *HERC2* may affect glioma predisposition and progression. Similarly, these aforementioned mutations and variations in the *HERC2* domain must be validated to understand their mechanistic insights and determine whether specific domains confer distinct gliomagenesis risk.

#### 4.1. Types of *HERC2* mutation

##### 4.1.1. Missense mutations

A missense mutation is a point mutation in which a single-nucleotide change results in a codon that codes for a different amino acid, altering the protein and its

corresponding structure and function.<sup>49</sup> A comprehensive whole-genome sequencing study involving 189 families with a history of glioma identified *HERC2* as the most significantly enriched gene harboring rare, deleterious variants. Specifically, six mutations were found: Five rare coding variants predicted to be highly deleterious single-nucleotide variants and one internal copy gain variant. These coding variants occurred in highly conserved regions of the gene, including domains critical for its function, such as the regulation of chromosome condensation and the homologous to the E6-AP C terminus (HECT) domain, and the researchers found marked selection against loss-of-function and missense mutation.<sup>18</sup> However, as noted earlier, *HERC2* is an extremely large protein (4,834 amino acids) that frequently harbors many variants in normal individuals.<sup>19</sup> It means, not all mutations in large genes, such as *HERC2*, are necessarily pathogenic, because the gene's size alone increases the statistical chance of harboring incidental (non-disease-causing) variants.

#### 4.1.2. Truncating mutations (loss-of-function, non-sense, frameshift, and splice-site mutation)

Truncating mutations are genetic alterations shortening the coding sequence of genes through ways like a stop-gain mutation, leading to a shortened or truncated protein.<sup>50</sup> Frattini *et al.*<sup>51</sup> discovered that truncating mutations in *HERC2* are localized on chromosome 15q13, commonly deleted and mutated, and have been implicated in gliomagenesis through multiple oncogenic mechanisms.<sup>51</sup> Loss-of-function mutations in *HERC2* can impair its ability to interact and regulate p53, facilitating failure of proper ubiquitination and recruitment of DNA repair proteins, notably those involved in ATM-dependent signaling, thereby compromising the DDR pathway.<sup>52</sup> This defect leads to the accumulation of unrepaired DNA damage, promoting genomic instability, a well-recognized driver of malignant progression in gliomas.<sup>53</sup> Non-sense mutations in *HERC2* – which are predicted to cause a frameshift insertion, leading to non-sense-mediated decay, or may otherwise be pathogenic and cause haploinsufficiency (i.e., a person with one functional copy of a gene leading to abnormal phenotype or disease) – were also identified in a familial glioma cohort.<sup>18,54</sup> While splice-site mutations are a recognized mechanism of gene disruption in gliomas, particularly in key tumor suppressors, such as *ATRX* and *TP53*, specific evidence for splice-site mutations in *HERC2* in glioma remains scarce, and further research is needed to clarify this association.<sup>55</sup>

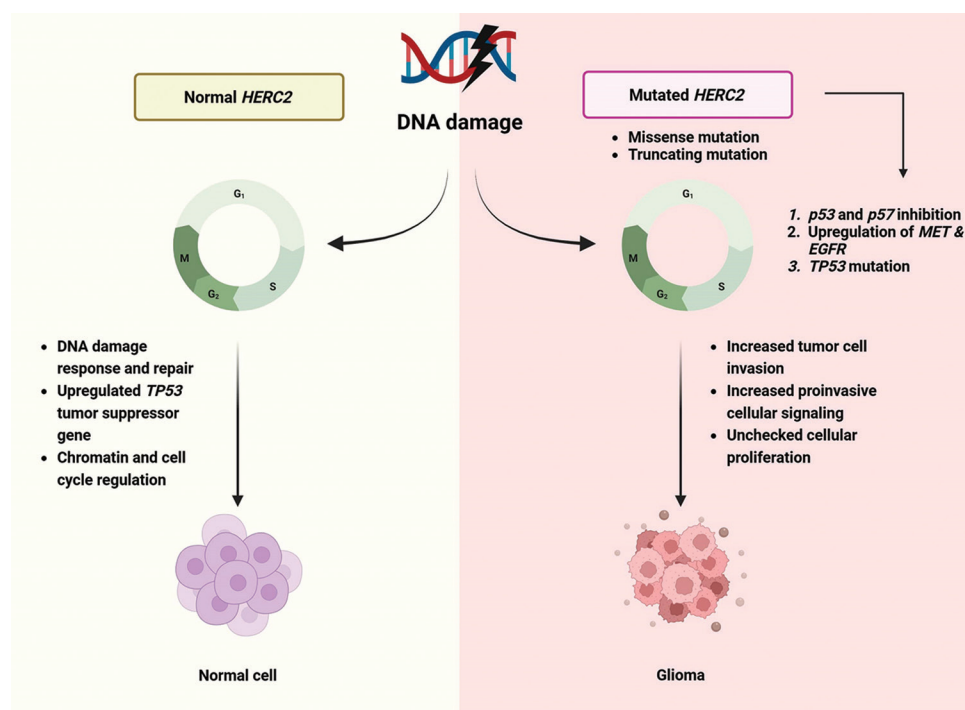
#### 4.2. *HERC2*-mediated *TP53* dysregulation in glioma cell proliferation

In gliomas, *TP53* mutations are particularly prevalent in lower-grade astrocytomas and secondary glioblastomas,

suggesting a role in early tumorigenesis and progression to more aggressive forms.<sup>56,57</sup> In addition, mutant p53 proteins can gain oncogenic functions, contributing to abnormal cell proliferation, altered metabolism, and resistance to therapy.<sup>58</sup> The disruption of p53-mediated transcriptional programs also interferes with the regulation of other critical pathways, including inhibition of p63 and p73, promoting tumor cell invasion, upregulating receptor tyrosine kinases, such as mesenchymal-epithelial transition and epidermal growth factor receptor, enhancing proinvasive cellular signaling.<sup>59-61</sup>

These findings suggest that *HERC2* mutations, particularly those impairing its structural domains or ubiquitin ligase activity, may facilitate gliomagenesis by compromising p53-mediated genome surveillance and promoting unchecked cellular proliferation (Figure 3). The convergence of *HERC2* dysfunction and *TP53* mutation may represent a cooperative oncogenic axis in familial glioma, highlighting the importance of exploring *HERC2* as a potential biomarker and therapeutic target, particularly in gene-directed therapies.

Functional validation studies also support the idea of how *HERC2* mutation leads to p53 dysfunction through oligomerization. An *in vitro* study by García-Cano *et al.*<sup>62</sup> using four different cell lines reveals that *HERC2* forms a complex with NEURL4, oligomeric p53, and mouse double minute 2 homolog, which stabilizes p53 and mouse double minute 2 homolog and regulates p53's transcriptional activity. Upon DNA damage induced by bleomycin, this complex dissociates, allowing p53 to become phosphorylated and acetylated, thereby enhancing its activity. *HERC2* also modulates *MDM2* gene expression through a p53-dependent mechanism by competing for binding with phosphorylated and acetylated p53 at the *MDM2* promoter.<sup>62</sup> Another *in vitro* study by Cubillos-Rojas *et al.*<sup>52</sup> supports the interaction of p53 and *HERC2* mutation. The researchers discovered that the HECT-type E3 ubiquitin ligase *HERC2* directly interacts with the tumor suppressor p53 through its conserved CPH domain, binding the C-terminal to the 43 amino acids of p53, and enhances p53's transcriptional activity by promoting p53 oligomerization, rather than affecting its stability. Silencing *HERC2* diminishes p53's ability to activate genes, such as *p21*, accelerates cell proliferation, and impairs p53-driven responses after DNA damage, revealing *HERC2* as a novel regulator of p53 signaling with implications for tumor suppression.<sup>52</sup> However, the functional validation studies conducted using non-glial cell lines (HeLa, HEK-293, U2OS, and H1299) highlight a limitation of the study, as confirming these findings in glial-specific models would provide more direct relevance to gliomagenesis.



**Figure 3.** Mechanism of normal and mutated *HERC2* in DNA repair during DNA damage. Created in BioRender. Relacion, P. (2025). <https://BioRender.com/ydgwau7>.

Abbreviations: EGFR: Epidermal growth factor receptor; MET: Mesenchymal-epithelial transition.

## 5. *HERC2* in the context of hereditary cancer syndromes

Hereditary cancer syndromes are a heterogeneous group of genetic diseases associated with a significantly increased risk of tumor development.<sup>63</sup> They have been traditionally associated with germline mutations in key genes responsible for maintaining genomic stability and DNA repair, such as *MSH2*, *MLH1*, and *BRCA1/2*.<sup>63,64</sup> While these classical familial cancer genes have been extensively studied and are well-characterized in syndromes, such as Lynch syndrome and hereditary breast/ovarian cancer, *HERC2* represents a more recently recognized multifunctional regulator involved in several tumorigenesis-related pathways, with a possible role in gliomagenesis.

Functionally, *MSH2* and *MLH1* are key components of the DNA mismatch repair (MMR) pathway, which is responsible for maintaining genomic integrity by correcting base-base mismatches and small insertion-deletion loops that occur during DNA replication.<sup>65</sup> Germline mutations in either gene impair the MMR system, resulting in the accumulation of errors, particularly within repetitive DNA sequences known as microsatellites (i.e., a phenomenon known as microsatellite instability). This instability substantially increases the risk of developing cancers, especially in the colorectal, gastric, and endometrial

tissues, and is a hallmark feature of Lynch syndrome.<sup>65</sup> Similarly, *BRCA1* and *BRCA2* play a crucial role in maintaining genomic stability by facilitating homologous recombination, a high-fidelity DNA repair mechanism responsible for accurately repairing double-strand breaks. Mutations in these genes impair repair of double-strand breaks, causing genomic instability, eventually resulting in oncogenic transformation of non-tumorigenic cells into tumor-initiating cells, and subsequently predisposing carriers to epithelial malignancies, such as breast, ovarian, and other cancers.<sup>66-68</sup>

In contrast to the more extensively characterized DNA repair genes, *HERC2*, an E3 ubiquitin ligase, regulates the stability and function of several key proteins involved in the DDR, including *BRCA1* and *p53*.<sup>52</sup> It also regulates the activity of proteins associated with homologous recombination and nucleotide excision repair pathways.<sup>22</sup> As such, *HERC2* is increasingly recognized as an important contributor in maintaining genomic stability, functioning similarly to *MSH2*, *MLH1*, and *BRCA1/2*. The multifaceted role of *HERC2* in DNA repair and tumor suppression suggests the possibility of a *HERC2*-associated cancer syndrome. Recent studies have implicated *HERC2* in familial glioma.<sup>18</sup> Moreover, *HERC2* mutations have been associated with neurodevelopmental disorders, such as Angelman-like syndrome and autism spectrum



disorder, indicating its broader role in cellular processes beyond DNA repair.<sup>69</sup> It is also important to consider that, due to *HERC2*'s interactions with key tumor suppressors, such as *BRCA1* and *p53*, its dysfunction may play a role in cancer predisposition syndromes, either overlapping with or distinct from established conditions, such as Li-Fraumeni or Lynch syndrome. The diverse functions of *HERC2* emphasize the importance of further investigation to better define the range of clinical phenotypes associated with its mutations.

## 6. Clinical and research implications of *HERC2* screening in familial glioma

The growing recognition of *HERC2* as a gene significantly enriched in familial glioma cohorts presents a promising opportunity to enhance current risk assessment and diagnostic frameworks for hereditary central nervous system tumors. While pathogenic germline mutations in genes, such as *MSH2*, *MLH1*, *BRCA1*, and *BRCA2* are already well-characterized with established penetrance rates and clinical guidelines, germline mutations in *HERC2* remain poorly defined.<sup>65,70</sup> As a result, standardized recommendations for genetic testing and clinical management are currently lacking. Nonetheless, the identification of *HERC2* as the most significantly enriched gene in familial glioma emphasizes its potential as a valuable genetic marker for glioma predisposition.<sup>18</sup> Familial glioma is rare (<5% of glioma cases) but carries a strong heritable risk. Known high-risk genes include those involved in telomere maintenance, such as *POT1*. Recent high-throughput sequencing studies, such as those by Nurminen *et al.*,<sup>71</sup> have expanded this list, revealing novel rare variants (*GALNT13*, *AR*, *MYO10*) in Finnish glioma families, further supporting a polygenic inheritance model where no single gene accounts for most cases.<sup>71</sup> Within this context, *HERC2* has emerged as one of the most significantly enriched genes in familial glioma cohorts, suggesting its potential as a biomarker for glioma susceptibility.<sup>18</sup>

From a clinical perspective, incorporating *HERC2* into multigene next-generation sequencing panels could improve early identification of at-risk individuals, guide targeted surveillance, and support cascade testing in families with unexplained glioma aggregation, particularly in the absence of pathogenic variants in established genes, such as *TP53*, *CDKN2A*, *IDH1/2*, and *MMR* genes.<sup>72,73</sup> If validated to confer increased glioma risk, *HERC2* could support risk stratification, especially in families where glioma presents with atypical features, such as early onset or unusual histologic subtypes. Its eventual utility could mirror that of *BRCA1/2* or *MMR* genes in hereditary cancer

syndromes, where identifying pathogenic variants enables predictive testing in asymptomatic relatives and risk-reducing strategies. Furthermore, *HERC2* screening could enable targeted research enrollment, allowing families with *HERC2* mutations to participate in longitudinal studies to define glioma penetrance, histologic spectrum, and outcomes.<sup>18,72</sup>

However, translation to clinical practice is challenging. *HERC2* is a large, highly polymorphic gene, and most healthy individuals carry multiple benign variants. Therefore, aggressive filtering and expert interpretation are essential to distinguish pathogenic mutations from benign polymorphisms. Moreover, known glioma risk genes still explain only a minority of familial cases, and no single variant has emerged as a common driver. Families often carry unique, rare variants, as illustrated in the Finnish cohort,<sup>71</sup> highlighting the polygenic and heterogeneous nature of familial glioma. As such, *HERC2* testing should be accompanied by careful genetic counseling, especially regarding variants of uncertain significance.

From a diagnostic standpoint, next-generation sequencing is becoming an integral component of routine neuropathological evaluation, especially with the growing demand for molecularly guided therapies. Tools, such as GliomaSCAN, a glioma-specific targeted next-generation sequencing panel developed by Shin *et al.*,<sup>74</sup> exemplify how somatic alterations can be identified with high accuracy.<sup>74</sup> Within this evolving landscape, *HERC2* warrants inclusion in glioma-specific panels due to its critical role in DDR, particularly in homologous recombination and nucleotide excision repair.<sup>22,52</sup> Germline *HERC2* variants may affect sensitivity to alkylating agents, such as temozolomide or influence radiation responses, highlighting their potential in personalized treatment planning. Technically, *HERC2* can be easily incorporated into existing hybrid-capture or amplicon-based next-generation sequencing platforms used for cancer predisposition screening.<sup>75</sup> However, interpretation challenges persist due to limited data on variant frequency, penetrance, and pathogenicity.

To support routine clinical implementation, robust genotype-phenotype correlation studies are essential. Resources, such as ClinVar, American College of Medical Genetics/Association for Molecular Pathology guidelines and *in silico* models offer a foundation for variant interpretation, but they must be supplemented with functional assays and population-level analyses to define *HERC2* variant expressivity and pathogenicity.<sup>76,77</sup> Future research should prioritize identifying glioma families with *HERC2* mutations to better delineate tumor subtypes, clinical penetrance, and biological mechanisms. Importantly, the practical utility of *HERC2* as a biomarker

depends not only on its statistical enrichment in familial glioma but also on evidence that its detection improves clinical outcomes through early intervention or tailored therapies.

From a research perspective, *HERC2*'s pleiotropic roles in p53 regulation, chromatin remodeling, and DNA damage signaling warrant investigation into its mechanistic role in gliomagenesis.<sup>22,52,69</sup> The integration of prospective clinical-genomic registries, functional studies, and pedigree-based investigations will be pivotal to determine the full clinical relevance of germline *HERC2* variants. Building a robust evidence base will be essential to validate *HERC2* as a glioma susceptibility gene and to inform future guidelines for genetic counseling, risk-adapted surveillance, and targeted preventive strategies in familial glioma.

## 7. *HERC2* in a therapeutic perspective

*HERC2* plays a key role in several critical DNA repair pathways, as previously discussed. Given this role, tumors with *HERC2* gene mutations may have a compromised ability to repair DNA damage effectively. This inherent deficiency could create a therapeutic vulnerability that can be exploited through synthetic lethality.<sup>78</sup> In synthetic lethality, the disruption of a single gene is compatible with cell survival, yet the simultaneous disruption of two or more specific genes leads to cell death. Thus, for glioma cells with *HERC2* mutations, inhibiting a second pathway that becomes essential for survival as *HERC2* defects could lead to tumor-specific cell death. The crucial role of *HERC2* in DNA repair mechanisms suggests that glioma cells with *HERC2* mutations might be especially susceptible to drugs that further disrupt the repair of damaged DNA. This opens promising avenues for the development of novel therapeutic strategies.

*HERC2*, as an E3 ubiquitin ligase, is inherently difficult to target with small molecule inhibitors, as E3-substrate interactions are transient and dynamic.<sup>79</sup> However, GDC-199 (also known as venetoclax), approved for chronic lymphocytic leukemia and small lymphocytic lymphoma, shows promise for more interventions in disrupting protein-protein interactions.<sup>80</sup> To overcome this challenge, future therapeutic interventions may focus on modulating its downstream pathways. For instance, RNF8 contributes to cancer chemoresistance and progression through the activation of the transcription factor Twist.<sup>81</sup> Thus, targeting RNF8 can be an effective strategy to combat tumor aggressiveness and undo its chemoresistance, which eventually turns a potential liability into an opportunity for therapeutics. Another example is the UBC13 (also known as UBE2N), a critical E2 ubiquitin-conjugating enzyme that is in tandem with RNF8 to produce signals

that prevent degradation and promote metastasis.<sup>47</sup> Small-molecule inhibitors, such as NSC697923 and BAY 11-7082 target UBC13 and thus validate its druggability.

Despite promising therapeutic possibilities, significant challenges exist in translating findings related to germline mutations to widespread adoption in clinical practice. Familial glioma itself is a relatively rare disease, and specific *HERC2* mutations within this already small subset of gliomas might be even less frequent, despite being the most significantly enhanced gene in recent analyses. This rarity presents a considerable hurdle for conducting larger-scale clinical trials, which are necessary for the rigorous evaluation of potential therapies. In addition, developing preclinical models that accurately reflect the complex genetic landscape of familial glioma, including the presence of specific *HERC2* mutations, is crucial in the early phases of drug development.

Apart from these considerations, the current lack of clear guidance on *HERC2* testing in glioma makes it challenging for genetic counselors to provide advice. Similar to other novel cancers, several dilemmas arise. These include how a discovery of a *HERC2* variant of unclear significance would change surveillance or prophylactic measures in relatives, and if findings with unconfirmed implications for disease pathogenesis should be disclosed to patients undergoing investigations.<sup>82</sup>

The rarity of familial glioma and the frequency of specific *HERC2* mutations within this group necessitate collaborative research efforts to overcome these challenges and ultimately translate research findings into meaningful clinical improvements for patients and their families. While the discovery of *HERC2* mutations is promising, further investigations are needed to ensure that the results are truly actionable.

## 8. Future perspectives

Although this study focuses on the role of *HERC2* in familial glioma, it is also important to investigate whether this gene plays a significant role in the more prevalent sporadic forms of the disease.<sup>18</sup> Analyzing the frequency of *HERC2* mutations and examining its expression levels in large cohorts of patients with sporadic gliomas could reveal its potential involvement in non-hereditary cases. A comprehensive understanding of *HERC2*'s role across different glioma subtypes and grades, as well as both familial and sporadic occurrences, will provide a more complete picture of its overall contribution to the development of gliomas.

Future research may further investigate penetrance, animal modeling, or biomarker development. However,

given limited resources, attention may be focused on further developing the exact model of *HERC2*-driven gliomagenesis through cellular or animal models. Further clarifying these links can lead to the identification of molecular targets to develop new and more precise interventions. Modeling efforts will clarify penetrance and natural history (informing risk estimates), identify biomarkers in the tumor and its microenvironment, and uncover druggable pathways. Interpretation of clinical observations and the design of pathway-targeted therapies would benefit from more solid biological foundations.

The new findings on *HERC2* add to the trend of leveraging DNA repair defects in cancer therapy. Like *BRCA1/2* in breast cancer, or MMR deficiency in colon cancer, *HERC2*-linked gliomas may define a set of brain tumors sensitive to DNA repair-related therapies and open therapeutic avenues for other cancers with similar *HERC2* mutations.<sup>35</sup> For example, the concept that loss of *HERC2* enhances the efficacy of CX-5461 may extend to other tumors with *HERC2* mutations.

## 9. Conclusion

This study highlights *HERC2* as a guardian of the genome with an important role in DNA damage repair, cell cycle regulation, and tumor suppression, in the context of familial glioma. Recently, whole-genome sequencing studies have identified *HERC2* as the most significantly enriched gene with rare, deleterious variants in familial glioma cohorts, suggesting a potential genetic predisposition previously unrecognized in glioma due to its predominantly sporadic nature.

As an E3 ubiquitin ligase, *HERC2* plays a central role in coordinating multiple DNA repair pathways, especially through its interactions with key proteins, such as p53, *BRCA1*, *RNF8*, and ubiquitin-specific peptidase 16. However, mutations, such as loss-of-function, truncating, or missense mutations in *HERC2* disrupt these pathways, resulting in genomic instability, impaired DNA repair, and unchecked cellular proliferation, considered hallmarks of tumorigenesis.

While *HERC2* mutations mirror dysfunctions in well-known glioma-associated genes, such as *TP53*, *ATRX*, and *IDH1*, it operates uniquely as an upstream regulator that modulates multiple tumor suppressor genes and repair mechanisms, making it a possible biomarker for familial glioma risk screening and a promising therapeutic target. However, cautious interpretation is required given *HERC2*'s size, polymorphic nature, and the rarity of familial glioma. More research is needed to determine the clinical significance, penetrance, and therapeutic implications of *HERC2* mutations.

In summary, this study underscores the emerging role of *HERC2* in familial glioma, with significant implications for diagnostics, prognosis, and targeted therapy; however, validation through broader investigation remains essential.

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The authors declare that they have no competing interests.

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*Conceptualization:* All authors

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