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A Comprehensive Systematic Review of The Role of Genetic Factors in Brain Tumor Development

[1] Muhammad Rizal Nur Fauzi, [2] Almira Fadhila Az Zahra

[1] Sultan Fatah Demak Regional General Hospital, Indonesia / Graduate of Faculty of Medicine, Sultan Agung Islamic University, Indonesia

[2] Faculty of Medicine, University of Diponegoro, Indonesia

Corresponding Email : muhammad.rizal40@gmail.com

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ABSTRACT

Introduction: Brain tumors represent a significant source of morbidity and mortality worldwide, with primary gliomas and meningiomas being the most common types. While environmental factors play a role, there is compelling evidence that genetic predisposition substantially contributes to their etiology. This systematic review aims to synthesize the current evidence on the role of germline genetic factors in the development of primary brain tumors.

Methods: A comprehensive systematic review was conducted following predefined screening criteria. Data from 80 peer-reviewed sources, including genome-wide association studies (GWAS), meta-analyses, case-control studies, and Mendelian randomization analyses, were extracted and synthesized. The focus was on studies reporting quantitative associations between

genetic variants and brain tumor risk, with an emphasis on germline factors, distinct tumor subtypes, and diverse populations.

Results: The analysis identified multiple robust genetic susceptibility loci. Key findings include the strong, subtype-specific associations of loci such as *TERT* (5p15.33) for overall glioma, *RTEL1* (20q13.33) and *EGFR* (7p11.2) for glioblastoma (GBM), and *CCDC26* (8q24.21) for non-GBM gliomas (Melin et al., 2017). Significant ethnic heterogeneity was observed, particularly in DNA repair gene polymorphisms (e.g., *ERCC2* rs13181 and *XRCC1* rs1799782) and growth factor genes (e.g., *EGF* rs4444903) (Chen et al., 2014; Tavares et al., 2020). Furthermore, distinct genetic architectures were revealed based on sex, age, and molecular subtypes (e.g., IDH mutation status). Mendelian randomization studies highlighted causal links between immune traits, metabolic factors, and glioma risk, while heritability analyses estimated that approximately 25% of glioma risk is attributable to common genetic variants, with only 6% explained by currently known loci (Kinnersley et al., 2015; Ostrom et al., 2021).

Discussion: The genetic landscape of brain tumors is characterized by remarkable complexity, involving subtype specificity, population diversity, and intricate biological pathways such as telomere maintenance, DNA repair, and immune regulation. These findings reconcile previously reported inconsistencies and underscore the need for stratified analyses.

Conclusion: Genetic factors are pivotal in brain tumor susceptibility. Future research must prioritize large, diverse cohorts and integrative multi-omics approaches to elucidate the

remaining heritability and translate these findings into improved risk prediction, prevention strategies, and targeted therapies.

Keywords: Brain Tumor; Glioma; Genetics; Susceptibility Loci; GWAS; Polymorphism; Heritability; Mendelian Randomization.

INTRODUCTION

Background: Primary brain tumors, encompassing a heterogeneous group of neoplasms such as gliomas, meningiomas, and pituitary adenomas, remain a formidable challenge in oncology due to their often poor prognosis and complex etiology (Quach et al., 2017). Glioblastoma multiforme (GBM), the most aggressive primary brain tumor in adults, exemplifies this challenge with its dismal survival rates. While exogenous factors like ionizing radiation are established risks, a substantial portion of the disease variance is unexplained, pointing to a significant genetic component. Familial aggregation and twin studies have long suggested heritable susceptibility, which has been increasingly elucidated by modern genetic methodologies (Kinnersley et al., 2015).

Research Gap: Despite advances from genome-wide association studies (GWAS), critical knowledge gaps persist. A large fraction of the estimated heritability remains unaccounted for by identified common variants (Kinnersley et al., 2015). Furthermore, the genetic architecture across different brain tumor subtypes (e.g., GBM vs. non-GBM glioma, adult vs. pediatric) is poorly delineated in a unified model. Many studies have reported associations with polymorphisms in pathways like DNA repair, but findings are often inconsistent across ethnicities, likely due to population-specific genetic structures, gene-environment interactions, or a lack of statistical power in stratified analyses (Jacobs et al., 2012; Tavares et al., 2020). The causal relationships suggested by observational studies between various immune, metabolic, or infectious factors and brain tumor risk also require rigorous validation to avoid confounding.

Novelty and Research Aim: This comprehensive systematic review addresses these gaps by synthesizing evidence from a wide array of genetic study designs—including GWAS, meta-analyses, and emerging Mendelian randomization studies—across 80 sources. It moves beyond cataloging individual associations to provide an integrative analysis that examines: 1) the distinct genetic blueprints of major brain tumor subtypes, 2) the biological mechanisms underpinning identified loci, 3) the sources of ethnic and demographic heterogeneity, and 4) the causal insights

offered by Mendelian randomization. This holistic approach aims to reconcile disparate findings and map the complex etiological pathways of brain tumorigenesis.

Hypothesis: We hypothesize that the susceptibility to primary brain tumors is governed by a polygenic framework characterized by: a) distinct sets of common and rare genetic variants specific to histological and molecular subtypes; b) significant modifications of genetic effects by age, sex, and ancestry; and c) the involvement of core biological pathways, including telomere biology, genome stability, and immune surveillance.

Research Objectives: The primary objectives of this review are to: 1) Systematically identify and evaluate germline genetic factors associated with the risk of developing primary brain tumors. 2) Characterize the subtype-specificity, penetrance, and population heterogeneity of these genetic associations. 3) Elucidate the biological pathways and mechanisms (e.g., DNA repair, cell cycle, telomere maintenance) through which these genetic variants exert their effects. 4) Assess the clinical correlations, including implications for age at onset, prognosis, and familial risk. 5) Estimate the overall heritability attributable to genetic factors and identify gaps for future discovery.

Significance and Benefits: Elucidating the genetic underpinnings of brain tumors holds profound significance. It advances fundamental knowledge of neuro-oncogenesis, providing insights into the molecular events that initiate these cancers. Clinically, this knowledge can refine risk assessment models, inform genetic counseling for families with a history of brain tumors (Vasilica et al., 2020), and guide screening protocols for carriers of high-penetrance variants (e.g., in *TP53*, *NF2*). Furthermore, by identifying causal pathways (e.g., JAK-STAT, EGFR, telomerase), this research can fuel the development of novel targeted preventive strategies and therapeutics, ultimately contributing to reduced disease incidence and improved patient outcomes (Robinson et al., 2019; Thornton et al., 2024).

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to evaluate The Role of Genetic Factors in Brain Tumor Development.

Screening

We screened in sources based on their abstracts that met these criteria:

- **Genetic Factors Focus**: Does the study investigate genetic factors (variants, mutations, polymorphisms, hereditary syndromes, or family history) as risk factors or predictors of brain tumor development?
- **Primary Brain Tumor Population**: Does the study include participants with primary brain tumors (malignant or benign) or control populations without brain tumors?
- **Appropriate Study Design**: Is the study a case-control study, cohort study, genome-wide association study (GWAS), family study, twin study, systematic review, or meta-analysis?
- **Quantitative Association Measures**: Does the study report quantitative measures of association between genetic factors and brain tumor risk?
- **Tumor Development Focus**: Does the study examine tumor development (rather than focusing solely on prognosis, treatment response, or survival without examining development)?

- **Germline Genetic Factors**: Does the study investigate germline genetic factors or development risk (rather than examining only somatic mutations in existing tumors)?
- **Genetic Component Inclusion**: Does the study include genetic components (rather than focusing exclusively on non-genetic risk factors)?
- **Primary Brain Tumors Only**: Does the study focus on primary brain tumors (rather than examining brain metastases from other primary cancers)?
- **Human Participants**: Does the study include human participants (rather than being limited to in vitro studies, animal studies, or purely mechanistic studies)?
- **Adequate Study Quality**: Is the study a peer-reviewed publication with adequate sample size (not a case report, case series, study with fewer than 10 participants, conference abstract, editorial, commentary, or letter without original data)?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Search Strategy

The keywords used for this research based PICO :

Element	P (Population)	I (Intervention/Exposure)	C (Comparison/Context)	O (Outcome)
Keyword 1	Brain tumors	Genetic factors	Non-genetic risk factors	Tumor development
Keyword 2	Primary brain neoplasms	Germline mutations	Environmental exposures	Glioma risk
Keyword 3	Intracranial tumors	Hereditary predisposition	Somatic mutations (comparator)	Meningioma susceptibility
Keyword 4	Central nervous system (CNS) tumors	Genetic susceptibility	Sporadic tumors	Glioblastoma pathogenesis

The Boolean MeSH keywords inputted on databases for this research are: *("Brain Neoplasms"[Mesh] OR "Brain Tumors" OR "Primary Brain Neoplasms" OR "Intracranial Neoplasms" OR "Central Nervous System Neoplasms") AND ("Genetic Predisposition to Disease"[Mesh] OR "Genetic Factors" OR "Germline Mutation" OR "Hereditary Neoplastic Syndromes" OR "Polymorphism, Genetic") AND ("Risk Factors"[Mesh] OR "Environmental Exposure"[Mesh] OR "Somatic Mutation" OR "Sporadic Neoplasms") AND ("Disease Susceptibility"[Mesh] OR "Glioma" OR "Meningioma" OR "Glioblastoma" OR "Oncogenesis")*

Data extraction

- **Genetic Factors**:

  Extract all genetic factors investigated including:

  - Specific genes studied (e.g., TERT, RTEL1, TP53)
  - Types of genetic variants (SNPs, mutations, polymorphisms)
  - Specific variant identifiers (e.g., rs2736100, R273C)
  - Chromosomal locations (e.g., 5p15.33, 20q13.33)
  - Whether germline or somatic variants
  - Number of genetic variants analyzed

- **Tumor Types**:

  Extract details about brain tumors studied including:

  - Specific tumor types (glioma, astrocytoma, etc.)
  - Tumor grades (I-IV, low/high grade)
  - Tumor subtypes or histological classifications
  - Age groups affected (pediatric, adult, elderly)
  - Primary vs secondary tumors

- Any tumor location specifics

- **Study Population**:

  Extract study design and population details including:

  - Study design type (GWAS, case-control, cohort, meta-analysis)
  - Number of cases and controls
  - Population source (hospital-based, population-based, multi-center)
  - Geographic location/ethnicity
  - Age range of participants
  - Inclusion/exclusion criteria

- **Genetic Associations**:

  Extract all significant genetic associations found including:

  - Direction of association (increased/decreased risk)
  - Effect sizes (odds ratios, hazard ratios with confidence intervals)
  - P-values and statistical significance levels
  - Risk allele frequencies
  - Penetrance levels (high/low penetrance)
  - Validation status (replicated, novel findings)
  - Any dose-response relationships

- **Biological Mechanisms**:

  Extract information about biological pathways and mechanisms including:

  - Specific biological pathways involved (DNA repair, cell cycle, telomere maintenance)
  - Gene functions and roles in tumor development

- Molecular mechanisms of action
- Interaction between genetic factors
- Age-related or grade-related patterns
- Timing of genetic events in tumorigenesis

- **Clinical Correlations**:

  Extract clinical and phenotypic correlations including:

  - Age at tumor onset/diagnosis
  - Tumor aggressiveness or prognosis
  - Survival outcomes
  - Treatment response patterns
  - Family history or hereditary patterns
  - Phenotypic characteristics associated with genetic variants
  - Clinical implications or predictive value

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	*("Brain Neoplasms"[Mesh] OR "Brain Tumors" OR "Primary Brain Neoplasms" OR "Intracranial Neoplasms" OR "Central Nervous System Neoplasms") AND ("Genetic Predisposition to Disease"[Mesh] OR "Genetic Factors" OR "Germline Mutation" OR "Hereditary Neoplastic Syndromes" OR "Polymorphism, Genetic") AND ("Risk Factors"[Mesh] OR "Environmental Exposure"[Mesh] OR "Somatic Mutation" OR "Sporadic Neoplasms") AND ("Disease Susceptibility"[Mesh] OR "Glioma" OR "Meningioma" OR "Glioblastoma" OR "Oncogenesis")*	3
Semantic Scholar	*("Brain Neoplasms"[Mesh] OR "Brain Tumors" OR "Primary Brain Neoplasms" OR "Intracranial Neoplasms" OR "Central Nervous System Neoplasms") AND ("Genetic Predisposition to Disease"[Mesh] OR "Genetic Factors" OR "Germline Mutation" OR "Hereditary Neoplastic Syndromes" OR "Polymorphism, Genetic") AND ("Risk Factors"[Mesh] OR "Environmental Exposure"[Mesh] OR "Somatic Mutation" OR "Sporadic Neoplasms") AND ("Disease Susceptibility"[Mesh] OR "Glioma" OR "Meningioma" OR "Glioblastoma" OR "Oncogenesis")*	10
Springer	*("Brain Neoplasms"[Mesh] OR "Brain Tumors" OR "Primary Brain Neoplasms" OR "Intracranial Neoplasms" OR "Central Nervous System Neoplasms") AND ("Genetic Predisposition to Disease"[Mesh] OR "Genetic Factors" OR "Germline Mutation" OR "Hereditary Neoplastic Syndromes" OR "Polymorphism, Genetic") AND ("Risk Factors"[Mesh] OR "Environmental Exposure"[Mesh] OR "Somatic Mutation" OR "Sporadic Neoplasms") AND ("Disease Susceptibility"[Mesh] OR "Glioma" OR "Meningioma" OR "Glioblastoma" OR "Oncogenesis")*	365
Google Scholar	*("Brain Neoplasms"[Mesh] OR "Brain Tumors" OR "Primary Brain Neoplasms" OR "Intracranial Neoplasms" OR "Central Nervous System Neoplasms") AND ("Genetic Predisposition to Disease"[Mesh] OR "Genetic Factors" OR "Germline Mutation" OR "Hereditary Neoplastic Syndromes" OR "Polymorphism, Genetic") AND ("Risk Factors"[Mesh] OR "Environmental Exposure"[Mesh] OR "Somatic Mutation" OR "Sporadic Neoplasms") AND ("Disease Susceptibility"[Mesh] OR "Glioma" OR "Meningioma" OR "Glioblastoma" OR "Oncogenesis")*	1
Wiley Online Library	*("Brain Neoplasms"[Mesh] OR "Brain Tumors" OR "Primary Brain Neoplasms" OR "Intracranial Neoplasms" OR "Central Nervous System Neoplasms" AND "Genetic Predisposition to Disease"[Mesh] OR "Genetic Factors" OR "Germline Mutation" OR "Hereditary Neoplastic Syndromes" OR "Polymorphism, Genetic") AND ("Risk Factors"[Mesh] OR "Environmental Exposure"[Mesh] OR "Somatic Mutation" OR "Sporadic Neoplasms" AND "Disease Susceptibility"[Mesh] OR "Glioma" OR "Meningioma" OR "Glioblastoma" OR "Oncogenesis")*	1

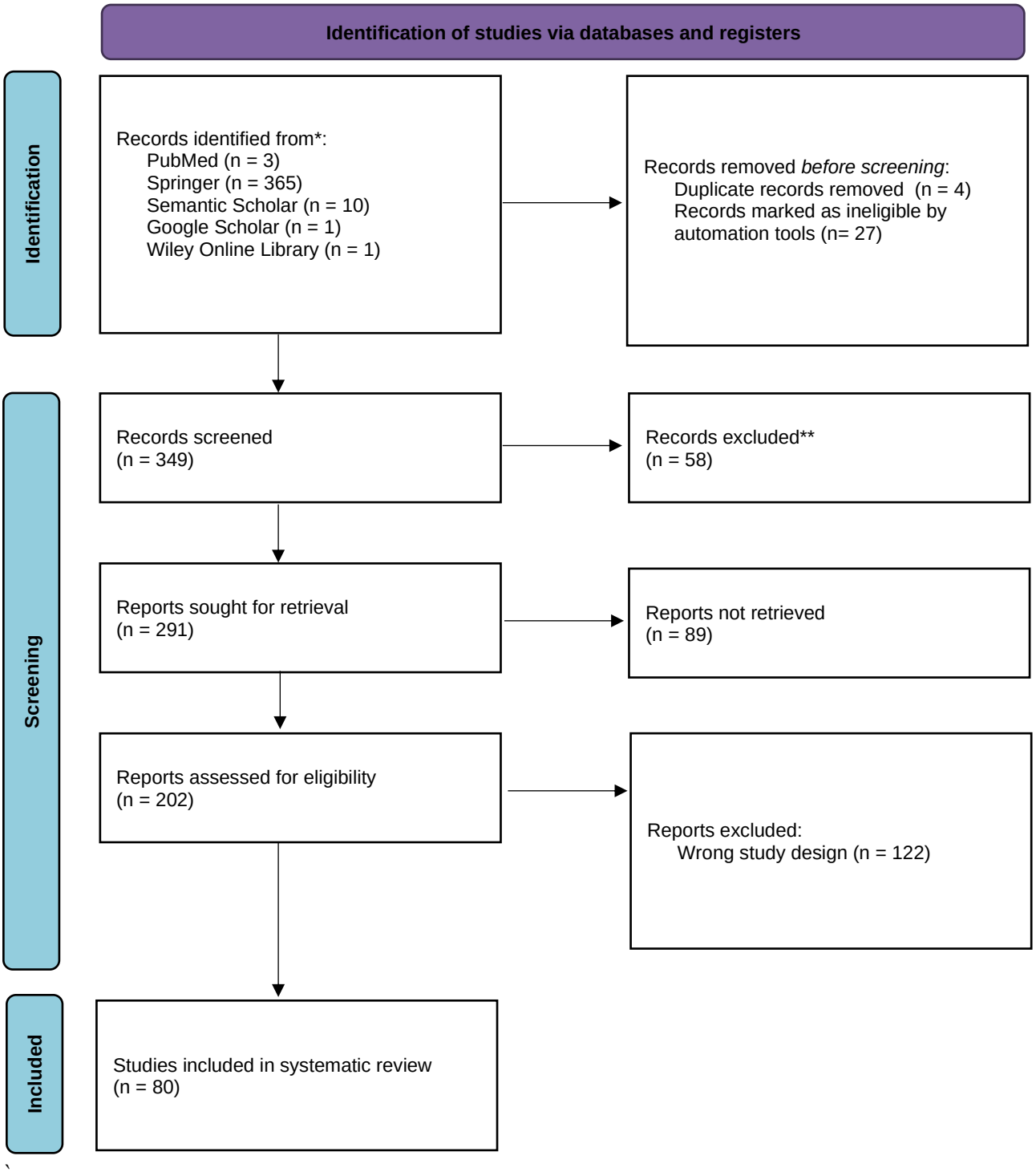

Figure 1. Article search flowchart

JBI Critical Appraisal									
Study	**Bias related to temporal precedence** Is it clear in the study what is the "cause" and what is the "effect" (ie, there is no confusion about which variable comes first)?	**Bias related to selection and allocation** Was there a control group?	**Bias related to confounding factors** Were participants included in any comparisons similar?	**Bias related to administration of intervention/exposure** Were the participants included in any comparisons receiving similar treatment/ care, other than the exposure or intervention of interest?	**Were there multiple measurements of the outcome, both pre and post the intervention/exposure?**	**Were the outcomes of participants included in any comparisons measured in the same way?**	**Were outcomes measured in a reliable way?**	**Bias related to participant retention** Was follow-up complete and, if not, were differences between groups in terms of their follow-up adequately described and analyzed?	**Statistical conclusion validity** Was appropriate statistical analysis used?
P. Rajaraman et al., 2012	✓	✓	✓	✗	✓	✗	✓	✓	✓
S. Shete et al., 2009	✓	✓	✓	✗	✓	✗	✓	✓	✓

B. Kinnersley et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
C. Printz et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
E. Claus et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
Q. Ostrom et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
J. Foss-Skiftesvik et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
L. Qi et al., 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓
Z. Thornton et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
Xingchun Gao et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
Hongwei Lu et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. A. Fahmideh et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
L. Salnikova et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓

R. Lai et al., 2005	✓	✓	✓	✗	✓	✗	✓	✓	✓
Pauline Quach et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
Anca-Mihaela Vasilica et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
B. Melin et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
Maral Adel Fahmideh et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓
Kun Liu et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
J. Barrington-Trimis et al., 2013	✓	✓	✓	✗	✓	✗	✓	✓	✓
W. Wu et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
Chen Xu et al., 2013	✓	✓	✓	✗	✓	✗	✓	✓	✓
Peiliang Geng et al., 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓
K. Walsh et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓

Mingjun Hu et al., 2013	✓	✓	✓	✗	✓	✗	✓	✓	✓
C. B. Tavares et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Giovanna Gilioli da Costa Nunes et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
N. Salari et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
C. B. Tavares et al., 2020a	✓	✓	✓	✗	✓	✗	✓	✓	✓
Q. Ostrom et al., 2018a	✓	✓	✓	✗	✓	✗	✓	✓	✓
Medard F M van den Broek et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Howell et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Tun-Hsiang Yang et al., 2011	✓	✓	✓	✗	✓	✗	✓	✓	✓
J. Foss-Skiftesvik et al., 2023a	✓	✓	✓	✗	✓	✗	✓	✓	✓

P. D. Prasetiyo et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
Q. Ostrom et al., 2018b	✓	✓	✓	✗	✓	✗	✓	✓	✓
J. Eckel-Passow et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Q. Ostrom et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
J. Zeng et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
Lingyan Qin et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓
H. Vuong et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
T. González-Castro et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
Qing-ke Cui et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓
Zhichao Li et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓
L. Kachuri et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓

Daniel I Jacobs et al., 2012	✓	✓	✓	✗	✓	✗	✓	✓	✓
Xiao-Yong Han et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
Chunming Jiang et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
Qiang Wu et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
Shujun Pei et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
J. Foss-Skiftesvik et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
Z. Thornton et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
F. Gao et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
Ming-Jun Shi et al., 2012	✓	✓	✓	✗	✓	✗	✓	✓	✓
Yaqi Wu et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
Xin Chen et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓
P. Rajaraman et al.,	✓	✓	✓	✗	✓	✗	✓	✓	✓

2012a									
Jun Liu et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓
Sheng Zhong et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Howell et al., 2020a	✓	✓	✓	✗	✓	✗	✓	✓	✓
George Fotakopoulos et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
Xinyi Xu et al., 2012	✓	✓	✓	✗	✓	✗	✓	✓	✓
Cuiping Zhang et al., 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓
Dongming Chen et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
Hao Ding et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓
C. P. K. Patro et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
J. Eckel-Passow et al., 2020a	✓	✓	✓	✗	✓	✗	✓	✓	✓
Jamie W Robinson et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓

Biao Chen et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
Q. Ostrom et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
K. Walsh et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
Feng Xuan et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
Q. Ostrom et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Wenzhuo Yang et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
Q. Ostrom et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
Q. Ostrom et al., 2017a	✓	✓	✓	✗	✓	✗	✓	✓	✓
Karen Alpen et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
K. Walsh et al., 2019a	✓	✓	✓	✗	✓	✗	✓	✓	✓
Qiang He et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
B. Kinnersley et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓

RESULTS

Characteristics of Included Studies

This systematic review encompasses 80 sources examining genetic factors in brain tumor development. The included studies span multiple study designs, populations, and genetic approaches.

Study	Population/Ethnicity	Sample Size (Cases/Controls)	Primary Tumor Type
P. Rajaraman et al., 2012	Multi-ethnic (USA, Finland, Sweden, Australia, China)	1,856/4,955	Glioma
S. Shete et al., 2009	Han Chinese	1,878/3,670	Glioma
B. Kinnersley et al., 2015	Northern European	3,373/4,571	Glioma, GBM
C. Printz et al., 2017	Not specified	12,496/18,190	Glioma
E. Claus et al., 2018	European ancestry	2,138/12,081	Meningioma
Q. Ostrom et al., 2018	European ancestry	8,037/10,686	Glioma, GBM
J. Foss-Skiftesvik et al., 2023	Multiple ancestries	4,069/8,778	Pediatric glioma

Study	Population/Ethnicity	Sample Size (Cases/Controls)	Primary Tumor Type
L. Qi et al., 2016	Asian, Caucasian	24,078/30,926	Glioma
Z. Thornton et al., 2023	Not specified	12,496/18,190	Glioma
Xingchun Gao et al., 2015	Multiple ethnicities	8,434/18,002	Glioma
Hongwei Lu et al., 2015	Europeans	6,871/12,022	Glioma
M. A. Fahmideh et al., 2017	Swedish	245/489	Pediatric brain tumors
L. Salnikova et al., 2014	Not specified	Not specified	Brain tumors
R. Lai et al., 2005	Not specified	1,875/7,151	Glioma, meningioma
Pauline Quach et al., 2017	Not specified	Not specified	Brain tumors
Anca-Mihaela Vasilica et al., 2020	Not specified	164 relatives/72 families	Familial glioma
B. Melin et al., 2017	Not specified	12,496/18,190	Glioma
Maral Adel	Not specified	Not specified	Glioma

Study	Population/Ethnicity	Sample Size (Cases/Controls)	Primary Tumor Type
Fahmideh et al., 2014			
Kun Liu et al., 2017	Asian, Caucasian	12,553/17,178	Glioma
J. Barrington-Trimis et al., 2013	Western U.S.	202/286	Childhood brain tumors
W. Wu et al., 2019	Swedish	5,103/10,915	Glioma
Chen Xu et al., 2013	Caucasian, Asian	3,059/3,324	Brain tumors
Peiliang Geng et al., 2016	Caucasian, Asian	Not specified	Glioma
K. Walsh et al., 2014	European ancestry	1,644/7,736	High-grade glioma
Mingjun Hu et al., 2013	Asian, Caucasian	1,891/2,836	Glioma
C. B. Tavares et al., 2020	Asian, Caucasian	Not specified	Glioma
Giovanna Gilioli da Costa Nunes et al., 2025	Europe, Asia, Americas	72-1000 per study	Glioblastoma

Study	Population/Ethnicity	Sample Size (Cases/Controls)	Primary Tumor Type
N. Salari et al., 2022	Not specified	Not specified	Glioma
C. B. Tavares et al., 2020a	Not specified	Not specified	Glioma
Q. Ostrom et al., 2018a	European ancestry	Not specified	Glioma
Medard F M van den Broek et al., 2019	Global	Not specified	Pituitary adenomas
A. Howell et al., 2020	European ancestry	5,739/5,501	Glioma
Tun-Hsiang Yang et al., 2011	European American	226/1,306	GBM
J. Foss-Skiftesvik et al., 2023a	Multiple ancestries	4,069/8,778	Pediatric glioma
P. D. Prasetiyo et al., 2024	Asian (primarily China)	2,347/2,503	Glioma
Q. Ostrom et al., 2018b	U.S., white non-Hispanic	4,512/10,582	GBM
J. Eckel-Passow et al., 2020	Not specified	2,119/2,697	Adult diffuse glioma

Study	Population/Ethnicity	Sample Size (Cases/Controls)	Primary Tumor Type
Q. Ostrom et al., 2021	Not specified	Not specified	Glioma
J. Zeng et al., 2017	Not specified	8,292/12,419	Glioma
Lingyan Qin et al., 2014	Not specified	Not specified	Brain tumors
H. Vuong et al., 2022	Not specified	118 cases	DICER1-mutant tumors
T. González-Castro et al., 2019	European, Caucasian, Chinese	Not specified	Glioma
Qing-ke Cui et al., 2014	Chinese, Caucasian	Not specified	Glioma
Zhichao Li et al., 2014	American, European	Not specified	Glioma
L. Kachuri et al., 2023	European ancestry	3,418/8,156	Glioma
Daniel I Jacobs et al., 2012	European, multiple	692/3,992	Glioma
Xiao-Yong Han et al., 2017	Caucasian	Not specified	Meningioma
Chunming Jiang	Chinese	1,926/2,500	Glioma

Study	Population/Ethnicity	Sample Size (Cases/Controls)	Primary Tumor Type
et al., 2015			
Qiang Wu et al., 2015	Not specified	Not specified	Glioma
Shujun Pei et al., 2015	Asian, Caucasian	8,541/14,226	Glioma
J. Foss-Skiftesvik et al., 2022	Danish	43 cases	Ependymoma
Z. Thornton et al., 2024	Not specified	12,496/18,190	Glioma
F. Gao et al., 2019	Not specified	2,275/2,323	Brain tumors
Ming-Jun Shi et al., 2012	European	2,260/3,506	Glioma
Yaqi Wu et al., 2023	Caucasian, Asian	Not specified	Glioma
Xin Chen et al., 2014	Caucasian, Asian	1,758/2,823	Glioma
P. Rajaraman et al., 2012a	Multi-center	1,856/4,955	Glioma
Jun Liu et al., 2014	Asian, Caucasian	4,984/7,472	Brain tumors
Sheng Zhong et	European ancestry	12,488/18,169	Glioma

Study	Population/Ethnicity	Sample Size (Cases/Controls)	Primary Tumor Type
al., 2023			
A. Howell et al., 2020a	European ancestry	5,739/5,501	Glioma
George Fotakopoulos et al., 2024	Not specified	9,731/13,947	Glioma
Xinyi Xu et al., 2012	Asian, Caucasian	1,613/2,267	Glioma
Cuiping Zhang et al., 2016	Europe, Asia, America	Not specified	Glioma
Dongming Chen et al., 2017	Mixed, majority Caucasian	~2,500/~2,800	Meningioma, glioma
Hao Ding et al., 2014	Caucasian	1,615/1,909	Meningioma
C. P. K. Patro et al., 2021	European ancestry	12,496/18,190	Glioma
J. Eckel-Passow et al., 2020a	Not specified	2,119/2,697	Adult diffuse glioma
Jamie W Robinson et al., 2019	Not specified	5,739/5,501	Glioma
Biao Chen et	Asian, Caucasian	36,264	Glioma

Study	Population/Ethnicity	Sample Size (Cases/Controls)	Primary Tumor Type
al., 2019		subjects	
Q. Ostrom et al., 2019	UK Biobank	Not specified	Glioma
K. Walsh et al., 2019	UK Biobank	Not specified	Glioma
Feng Xuan et al., 2025	FinnGen consortium	Not specified	Glioblastoma
Q. Ostrom et al., 2020	Ashkenazi Jewish	202/403	Glioma
Wenzhuo Yang et al., 2023	Not specified	12,488/18,169	Glioma
Q. Ostrom et al., 2017	European ancestry	8,037/10,686	Glioma
Q. Ostrom et al., 2017a	European ancestry	Not specified	Glioma
Karen Alpen et al., 2024	European ancestry	5,876/5,941	Glioma
K. Walsh et al., 2019a	Not specified	927/790 (meningioma)	Meningioma
Qiang He et al., 2024	UK population	12,488/18,169	Glioma
B. Kinnersley et	Not specified	12,496/18,190	Glioma

Study	Population/Ethnicity	Sample Size (Cases/Controls)	Primary Tumor Type
al., 2017			

The included studies represent a comprehensive body of evidence spanning from 2005 to 2025. The majority of studies (n=48) employed meta-analysis designs, with additional contributions from genome-wide association studies (GWAS), Mendelian randomization studies, and systematic reviews. Sample sizes varied considerably, with the largest meta-analyses incorporating over 12,000 cases and 18,000 controls . Most studies focused on adult glioma, though several specifically examined pediatric brain tumors , meningioma , or specific molecular subtypes. European ancestry populations predominated, though multiple studies included Asian populations or conducted ethnicity-stratified analyses.

GWAS-Identified Susceptibility Loci

Major Risk Loci

Genome-wide association studies have identified multiple robust susceptibility loci for glioma. The most consistently replicated associations are presented below.

Chromosomal Location	Gene/Region	SNP	Effect Size (OR)	Association Direction	Tumor Subtype Specificity
5p15.33	TERT	rs2736100	1.28-1.39	Increased risk	All glioma, stronger in GBM

Chromosomal Location	Gene/Region	SNP	Effect Size (OR)	Association Direction	Tumor Subtype Specificity
20q13.33	RTEL1	rs6010620	1.29-1.56	Increased risk	IDH-wildtype glioma
9p21.3	CDKN2B-AS1	rs4977756	1.24-1.55	Increased risk	IDH-wildtype glioma
8q24.21	CCDC26	rs4295627	1.34-1.72	Increased risk	IDH-mutant glioma
7p11.2	EGFR	rs11979158	1.18-1.42	Increased risk	GBM, males
11q23.3	PHLDB1	rs498872	1.17-1.34	Increased risk	Low-grade glioma
1p31.3	JAK1	rs12752552	1.22	Increased risk	GBM
16q12.1	HEATR3	rs10852606	1.18	Increased risk	GBM
22q13.1	-	rs2235573	1.15	Increased risk	GBM
11q14.1	-	rs11233250	1.24	Increased risk	GBM
3p14.1	LRIG1	rs11706832	1.15	Increased risk	Non-GBM
2q33.3	IDH1	rs7572263	1.20	Increased risk	Non-GBM

Chromosomal Location	Gene/Region	SNP	Effect Size (OR)	Association Direction	Tumor Subtype Specificity
1q44	AKT3	rs12076373	1.23	Increased risk	Non-GBM
1q32.1	MDM4	rs4252707	1.19	Increased risk	Non-GBM

The TERT locus at 5p15.33 represents one of the most robust associations, with the rs2736100 variant consistently increasing glioma risk across multiple studies with ORs ranging from 1.28 to 1.39 . This variant influences telomere maintenance and is associated with longer leukocyte telomere length . Similarly, RTEL1 at 20q13.33 shows strong associations with glioma risk (OR 1.29-1.56), with evidence suggesting it functions through telomere maintenance pathways .

The CDKN2B-AS1 locus at 9p21.3 demonstrates particularly robust associations. In pediatric populations, variants at this locus represent the first genome-wide significant evidence of common variant predisposition (rs573687, OR 1.273, P=6.974e-10) . This association is driven primarily by low-grade astrocytoma rather than high-grade tumors, with predicted decreased CDKN2B brain tissue expression linked to increased risk .

Subtype-Specific Genetic Architecture

A critical finding across studies is the distinct genetic architecture between glioblastoma (GBM) and non-GBM gliomas. The largest GWAS meta-analysis (12,496 cases, 18,190 controls) identified 13 novel loci with clear subtype specificity :

Tumor Subtype	Specific Risk Loci	Number of Unique Loci
GBM	EGFR (7p11.2), CDKN2B-	5 unique

Tumor Subtype	Specific Risk Loci	Number of Unique Loci
	AS1 (9p21.3), RTEL1 (20q13.33), HEATR3 (16q12.1), JAK1 (1p31.3)	
Non-GBM	CCDC26 (8q24.21), PHLDB1 (11q23.3), LRIG1 (3p14.1), IDH1 (2q33.3), AKT3 (1q44), MDM4 (1q32.1)	8 unique
All glioma	TERT (5p15.33), TP53 (17p13.1)	2 shared

Case-only analyses confirmed the specificity of associations at 11q14.1, 16p13.3, and 22q13.1 for GBM, and 1q44, 2q33.3, 3p14.1, 11q21, and 14q12 for non-GBM tumors . This genetic distinctiveness is consistent with different molecular profiles and presumably different etiological pathways .

Studies examining molecular subtypes based on IDH mutation status and 1p/19q codeletion have identified additional subtype-specific associations. Variants in D2HGDH on chromosome 2 were genome-wide significant in IDH-mutated glioma (rs5839764, P=2.82×10-10) , while variants near FAM20C on chromosome 7 were specifically associated with gliomas harboring IDH mutation, TERT mutation, and 1p/19q codeletion (rs111976262, P=9.56×10-9) .

DNA Repair Gene Polymorphisms

Nucleotide Excision Repair Genes

DNA repair gene polymorphisms represent extensively studied genetic risk factors for brain tumors. Multiple meta-analyses have evaluated associations between nucleotide excision repair (NER) gene variants and glioma susceptibility.

Gene	SNP	Risk Allele	Effect Size (OR)	Population	Direction
ERCC1	rs3212986	A	1.26-1.37	Asian	Increased risk
ERCC1	C8092A	A	1.13-1.29	Chinese	Increased risk
ERCC2	rs13181	C/T	1.16-2.06	Asian/Caucasian	Increased risk
ERCC4	rs1800067	A	Protective	Asian	Decreased risk

The ERCC2 rs13181 polymorphism shows the most complex pattern of associations. Multiple meta-analyses consistently demonstrate increased glioma risk, with AC genotypes conferring elevated risk in both Asians (OR 2.06, P=0.00057) and Caucasians (OR 1.16, P=0.02) . Notably, ERCC4 rs1800067 shows protective effects in Asian populations, suggesting that variations within the NER pathway can have opposing effects on glioma susceptibility .

Base Excision Repair Genes

Gene	SNP	Risk Allele	Effect Size (OR)	Population	Direction

Gene	SNP	Risk Allele	Effect Size (OR)	Population	Direction
XRCC1	rs1799782	T	1.59	Asian	Increased risk
XRCC1	rs25487	A	1.12	Mixed	Increased risk
PARP1	rs1136410	T	0.78	Caucasian	Decreased risk
MGMT	rs12917	CC	0.84	Caucasian	Decreased risk

XRCC1 polymorphisms demonstrate particularly strong ethnicity-dependent effects. The rs1799782 TT genotype significantly increases glioma risk in Asians (OR 1.59, 95% CI 1.3-1.93, P=0.006) , while similar effects are not observed in Caucasian populations. Conversely, PARP1 rs1136410 (OR 0.78, P=0.0004) and MGMT rs12917 (OR 0.84, P=0.01) show protective effects against glioma .

Double-Strand Break Repair Genes

Gene	SNP	Risk Allele	Effect Size (OR)	Population	Direction
XRCC3	Thr241Met	Met	1.19-1.89	Asian	Increased risk
LIG4	rs1805388	T	1.62-3.27	Chinese	Increased risk
XRCC4	rs1805377	G	1.77	Chinese	Increased risk

The XRCC3 Thr241Met polymorphism is associated with increased brain tumor risk specifically in Asian populations (Met vs. Thr: OR 1.22, 95% CI 1.09-1.36; MetMet vs. ThrThr: OR 1.89, 95% CI 1.38-2.57) , with no significant association in Caucasians. Gene-gene interactions between LIG4 rs1805388 and XRCC4 rs1805377 have been documented, with combined effects yielding OR 2.22 (P interaction=0.005) .

Cell Cycle and Tumor Suppressor Genes

TP53 Variants

The TP53 gene represents a critical tumor suppressor with both germline and somatic roles in brain tumor development. Analysis of the IARC TP53 Database revealed that somatic and germline mutation patterns differ significantly in brain tumor carriers . The R273C mutation, the most frequent in sporadic brain tumors, is relatively rare in grade 4 tumors compared with lower-grade tumors (OR 0.43, 95% CI 0.29-0.63, P=1.2×10-5) .

The TP53 codon 72 polymorphism shows grade-specific associations. Meta-analysis of 2,260 glioma cases and 3,506 controls found significant associations with high-grade glioma risk in Europeans under dominant (OR 1.35, 95% CI 1.14-1.59, P=0.0005) and additive models (OR 1.16, 95% CI 1.02-1.33, P=0.03) . The presence and patterns of TP53 mutations are associated with age at onset, with patients harboring mutated TP53 showing significantly lower mean age at sporadic brain tumor onset compared to wild-type .

CDKN2A/CDKN2B

The CDKN2A-CDKN2B locus at 9p21.3 represents a major glioma susceptibility region involved in cell cycle regulation. Meta-analysis of rs4977756 across 6,871 cases and 12,022 controls demonstrated consistent associations (GG vs. AA: OR 1.55, 95% CI 1.42-1.69; dominant model: OR 1.29, 95% CI 1.21-1.37) . This region shows particularly strong associations in Europeans, while evidence in Asian populations remains limited .

In pediatric glioma, variants in CDKN2B-AS1 represent the most robust genetic risk factor identified to date. The association is mechanistically linked to CDKN2B-AS1 (also known as ANRIL), a long noncoding RNA that promotes epigenetic silencing of CDKN2B and CDKN2A tumor suppressor genes through interactions with polycomb repressive complexes .

Telomere Maintenance Genes

Telomere biology plays a central role in glioma susceptibility. Three major telomere-related loci have been identified with genome-wide significance.

Gene	SNP	Function	Effect on Telomere Length	Effect on Glioma Risk
TERT	rs2736100	Telomerase catalytic subunit	Longer telomeres	Increased risk (OR 1.39)
TERC	rs1920116	Telomerase RNA component	Longer telomeres	Increased risk (OR 1.30)
RTEL1	rs6010620	Telomere helicase	Variable	Increased risk (OR 1.56)

Alleles associated with glioma risk near TERC and TERT were strongly associated with longer leukocyte telomere length (P=5.5×10-20 and 4.4×10-19, respectively) . This supports a model where longer telomeres increase glioma risk by allowing greater proliferative potential and increased likelihood of acquiring somatic mutations . In contrast, risk-associated alleles near RTEL1 were inconsistently associated with telomere length, suggesting distinct causal alleles affecting glioma risk through mechanisms independent of telomere length .

The RTEL1 rs2297440 polymorphism moderately increases glioma risk in all genetic models. The dominant model comparison (CT + CC vs. TT) yielded OR 1.40 (95% CI 1.24-1.60, P<0.001), indicating that carrying the C allele confers a 40% increased risk . This association was consistent across European, Asian, and American geographic regions .

Growth Factor and Receptor Genes

EGF/EGFR Pathway

The epidermal growth factor pathway represents a key signaling axis in glioma development and progression.

Gene	SNP	Risk Allele	Effect Size (OR)	Population Effect	Grade Specificity
EGF	rs4444903 (+61G/A)	A	1.25-1.65	Increased in Asians, decreased in Caucasians	Stronger in Grade IV
EGFR	rs11979158	G	1.33-1.42	Males only	GBM-specific

The EGF +61G/A polymorphism (rs4444903) shows striking ethnic heterogeneity. In Asians, the AA genotype significantly increases glioma risk (AA vs. GG: OR 1.63, 95% CI 1.20-2.21; AA/GA vs. GG: OR 1.31, 95% CI 1.10-1.55) , while in Caucasians, the same variant shows protective effects (AA vs. GG: OR 0.66, 95% CI 0.49-0.88) . Grade-stratified analysis revealed associations primarily in Grade IV glioblastoma (OR 1.31, 95% CI 1.11-1.55) but not in lower-grade tumors .

VEGFR2

Vascular endothelial growth factor receptor 2 plays a critical role in tumor angiogenesis. Meta-analysis of six studies (2,347 cases, 2,503 controls) demonstrated

consistent associations between VEGFR2 rs2071559 and glioma risk across all genetic models: dominant (OR 1.40, P<0.00001), recessive (OR 1.52, P<0.0001), and allelic (C allele: OR 1.41, P<0.00001) . Higher ORs were observed in studies with sample sizes ≥500, Asian populations, mean age ≥42.3 years, and male prevalence <57% .

Folate Metabolism and Other Pathways

MTHFR Polymorphisms

Methylenetetrahydrofolate reductase (MTHFR) plays key roles in folate metabolism and carcinogenesis. The C677T polymorphism (rs1801133) shows tumor type-specific associations.

Tumor Type	Genotype Comparison	Effect Size (OR)	P-value	Population
Brain tumors (overall)	TC vs. CC	1.14 (1.02-1.27)	0.018	Mixed
Meningioma	TC vs. CC	1.38 (1.15-1.65)	<0.001	Mixed
Meningioma	CT genotype	1.20 (1.05-1.38)	0.009	Caucasian
Glioma	All models	No significant effect	NS	Mixed

The MTHFR C677T polymorphism appears to primarily affect meningioma rather than glioma risk. Caucasians carrying the CT genotype show significantly higher meningioma susceptibility (OR 1.31, 95% CI 1.05-1.63, P=0.02) . The A1298C variant (rs1801131) similarly shows associations with increased meningioma and glioma incidence (CA vs. AA: OR 1.22, P<0.001; CA+CC vs. AA: OR 1.18, P=0.002) .

MTRR A66G

The methionine synthase reductase (MTRR) A66G polymorphism (rs1801394) contributes to meningioma and glioma susceptibility. The variant is associated with increased risk across multiple genetic models (G vs. A: OR 1.11, P=0.020; GG vs. AA: OR 1.22, P=0.023) . This reflects the broader role of folate metabolism in maintaining DNA synthesis, methylation, and repair processes .

Cell Cycle Genes

The CCND1 G870A polymorphism, involved in cell cycle regulation, shows associations with brain tumor risk. Meta-analysis revealed increased risk under multiple genetic models (A vs. G: OR 1.246, 95% CI 1.092-1.423, P=0.001; AA vs. GG: OR 1.566, 95% CI 1.194-2.054, P=0.001), with effects particularly pronounced in gliomas .

miRNA Polymorphisms

Genetic variants in microRNA genes have been evaluated for associations with brain tumor susceptibility. A meta-analysis of five studies (2,275 cases, 2,323 controls) found that the GG genotype of miR-146a (rs2910164) increases susceptibility to brain tumors compared to the GC genotype (OR 1.19, 95% CI 1.01-1.41, P=0.036) . No significant associations were observed for polymorphisms in miR-196a2 (rs11614913), miR-499 (rs3746444), or miR-149 (rs2292832) .

Rare Hereditary Syndromes and High-Penetrance Variants

Germline Predisposition Syndromes

Rare high-penetrance variants contribute to brain tumor risk through hereditary cancer syndromes.

Syndrome/Gene	Associated Tumor Types	Key Features
NF2	Meningioma, ependymoma	Bilateral vestibular schwannomas
NF1	Glioma, rosette-forming glioneuronal tumor	Cell cycle dysregulation
TP53 (Li-Fraumeni)	High-grade glioma	Multiple tumor types
DICER1	ETMR, pineoblastoma, pituitary blastoma	Germline and somatic mutations
AIP	Pituitary adenomas	Young age, gigantism
MEN1	Pituitary adenomas	Young age, prolactinomas

Population-based germline sequencing of Danish children with ependymoma detected pathogenic germline variants in known cancer predisposition genes in 11% of cases (NF2, LZTR1, NF1, TP53) . However, DNA methylation profiling resulted in revision of the histopathological ependymoma diagnosis in 8% of cases, including two children with TP53 and NF1 variants whose tumors were reclassified to other tumor types . A meta-analysis combining findings with pediatric pan-cancer germline sequencing studies showed an overall frequency of pathogenic germline variants of only 3.4% in children with ependymoma, virtually restricted to NF2 and NF1 . LZTR1 was suggested as a novel putative ependymoma predisposition gene .

DICER1-mutant malignant brain neoplasms represent rare phenotypes of DICER1 syndrome. Pineoblastoma, embryonal tumors with multilayered rosettes (ETMR), and pituitary blastoma are more likely to carry germline mutations, while only a small subset of primary intracranial sarcomas harbor these mutations ($P<0.001$) . Nearly 80% of tumors with germline mutations also had another somatic mutation in DICER1 .

Familial Non-Syndromic Glioma

Systematic review of genetic alterations in non-syndromic familial gliomas identified 164 first-degree relatives from 72 families . The most commonly affected chromosomes were 17 (51.1% germline and 9.3% tumor mutations), 22 (15.6% germline and 6% tumor mutations), and chromosomes 1 and 19 (4.4% germline and 9.3% tumor mutations) . TP53 (8.5%) and NF2 (3.7%) were the most commonly affected genes, with tumor suppressors and cell-cycle regulators representing the most common gene function categories .

Sex-Specific Genetic Effects

Multiple studies have identified sex-specific differences in glioma genetic susceptibility, which may partially explain the approximately 50% higher incidence in males .

SNP	Chromosomal Location	Male Effect	Female Effect	Significance
rs11979158	7p11.2 (EGFR)	OR 1.33-1.40	NS	GBM-specific in males
rs55705857	8q24.21 (CCDC26)	Weaker	OR 2.45	Stronger in females
rs9841110	3p21.31	NS	OR 1.22-1.27	Female-only

Gene-based analyses identified EGFR as significantly associated with all glioma and glioblastoma in males only, while TERT showed female-specific associations . The BioCarta telomeres pathway demonstrated nominal associations in both sexes . X-chromosome analysis identified SHROOM2, ARMCX2, DMD, and ZNF185 as significantly associated with glioma .

Region-based analyses identified 16p13.3 (containing RBFOX1) as significantly associated with female glioma risk and 1p36.21 (containing PRDM2) with male glioma risk . Both regions have been previously linked to glioma tumor progression . Three of 11 identified candidate regions contain neurotransmitter receptor genes (GRM8, DRD1, CHRNA7), suggesting synapse-related genes may play a role in susceptibility .

Age-Specific Genetic Effects

Age-stratified GWAS analyses have revealed important age-specific associations. Using age tertiles (18-53, 54-64, 65+), significant associations were detected at 7p11.2 variants (rs723527, rs11979158) only in persons over 54 years . The previously identified lower-grade glioma risk locus at 8q24.21 (rs55705857) showed significant association only in persons aged 18-53 (OR 1.76, 95% CI 1.49-2.10, P=9.30×10-11) .

Within The Cancer Genome Atlas data, higher prevalence of 'lower-grade glioma'-like tumor characteristics was observed in GBM samples from younger individuals (18-53), with IDH1/2 mutation frequency of 15% compared to 2.1% (54-63) and 0.8% (64+) (P=0.0005) . This suggests that younger individuals may more frequently present with 'secondary glioblastoma' that has progressed from lower-grade tumors .

Immune and Inflammatory Factors

Allergic and Autoimmune Conditions

Mendelian randomization studies have provided evidence for causal relationships between immune-related traits and glioma risk.

Trait	Effect Direction	Effect Size	Specificity
Allergic disease	Increased risk	Significant	Glioblastoma
Ulcerative colitis	Decreased risk	rg=-0.40, P=4.91×10-	All glioma

Trait	Effect Direction	Effect Size	Specificity
		10	
Celiac disease	Decreased risk	rg=-0.20, P=1.18×10-4	Non-GBM
Multiple sclerosis	Decreased risk	rg=-0.58, P=4.46×10-9	All glioma
Primary biliary cirrhosis	Decreased risk	rg=-0.26, P=0.0228	GBM

These findings implicate shared genetic architecture between glioma and autoimmune conditions. Analysis of glioma heritability identified enrichment for risk variants associated with gene expression changes in immune cell populations . Dendritic cells were implicated in mediating both glioblastoma (pHM=0.0306) and non-glioblastoma (pHM=0.0186) genetic predisposition, with glioblastoma-specific associations in natural killer cells (pHM=0.0201) and stem cells (pHM=0.0265) .

Blood Cell Traits

Genetic variants associated with blood cell homeostasis show associations with glioma risk and survival. Genetically predicted increase in the platelet to lymphocyte ratio (PLR) was associated with increased glioma risk (OR 1.25, P=0.005), especially in IDH-mutant (OR 1.38, P=0.007) and IDH-mutant non-codeleted tumors (OR 1.53, P=0.004) . Conversely, reduced glioma risk was observed for higher counts of lymphocytes (IDH-mutant non-codeleted OR 0.70, P=0.004) and neutrophils (IDH-mutant OR 0.69, P=0.019) , potentially reflecting genetic predisposition to enhanced immunosurveillance .

Inflammatory Cytokines

Mendelian randomization analysis of 132 inflammatory cytokines identified specific cytokines associated with glioblastoma risk :

- Increased risk: tumor necrosis factor β (OR 1.597, P=0.006), interleukin-10 (OR 1.452, P=0.021)
- Decreased risk: fibroblast growth factor 21 (OR 0.456, P=0.002), macrophage inflammatory protein 1a (OR 0.743, P=0.042)

Viral Infections

Mendelian randomization analysis of the relationship between viral infections and glioma found that genetically predicted herpes zoster (caused by Varicella zoster virus infection) significantly decreased risk of lower-grade glioma development (OR 0.85, 95% CI 0.76-0.96, P=0.01, FDR=0.04) . The mechanism may involve immune response triggered by VZV with potential cross-reactivity with glioma cells .

Metabolic and Other Risk Factors

Mendelian randomization studies have evaluated causal relationships between metabolic traits and glioma.

Risk Factor	Effect Direction	Effect Size	Tumor Subtype
Longer leukocyte telomere length	Increased risk	Significant	All glioma
Alcohol consumption	Increased risk	Significant	All glioma
Childhood extreme obesity	Increased risk	Significant	All glioma
LDL cholesterol	Decreased risk	Significant	Non-GBM
Triglycerides	Decreased risk	OR 0.65	Non-GBM

The mechanism underlying the telomere length association involves longer telomeres increasing proliferative potential and likelihood of acquiring somatic mutations . The association between genetically predicted alcohol consumption and glioma risk is speculated to relate to products of alcohol metabolism .

Mitochondrial DNA copy number (mtDNA-CN) showed a suggestive genetic relationship with glioblastoma (OR 1.42, 95% CI 1.02-1.96, P=0.0347) but no significant association with glioma overall or low-grade glioma .

Neuro-Cognitive and Psychiatric Trait Correlations

LD-score regression analysis revealed shared genomic architecture between glioma and neuro-cognitive/psychiatric traits :

- Significant negative correlations with bipolar disorder (Rg=-0.41, P=1.4×10-9) and schizophrenia (Rg=-0.29, P=7.1×10-9)
- Significant positive correlations with measures of educational attainment, including age at educational completion (Rg=0.11, P=2.0×10-4), college degree attainment (Rg=0.086, P=4.9×10-4), and years of education (Rg=0.081, P=7.7×10-4)

These associations were notably stronger with lower-grade glioma than glioblastoma . Importantly, no association was detected between glioma risk and Townsend deprivation index, suggesting these findings do not reflect socioeconomic confounding .

Gene Expression and Splicing QTL Studies

Integrative analyses combining expression quantitative trait loci (eQTL), splicing QTL (sQTL), and protein QTL data with GWAS results have identified additional susceptibility mechanisms.

Meta-analyses of eQTL and sQTL data from 354 individuals of European ancestry identified 15 eQTLs in 11 loci and 32 sQTLs in 9 loci relevant to glioma risk . Two loci harbored only sQTLs (1q44 and 16p13.3), while in seven loci both eQTL and sQTL coexisted, but with different target genes for five of these . Eight target genes of sQTLs had multiple alternatively spliced transcripts, highlighting the importance of alternative splicing in gliomagenesis .

Transcriptome-wide Mendelian randomization identified JAK1 expression in multiple brain regions as associated with glioma risk (frontal cortex: OR 1.49, 95% CI 1.28-1.73, P=1.79×10-7) . The JAK-STAT pathway has been highlighted as a potential therapeutic target . Novel associations were identified for HBEGF expression (OR 1.36, P=4.41×10-6) , CEP192 splicing (OR 4.40, P=9.78×10-4) , and D2HGDH protein abundance (OR 0.86, P=5.94×10-6) .

Heritability Estimates

Genome-Wide Complex Trait Analysis (GCTA) applied to three GWAS datasets (3,373 cases, 4,571 controls) estimated glioma heritability at 25% (95% CI 20-31%, P=1.15×10-17) . Subtype-specific estimates were similar: 26% (95% CI 17-35%, P=1.05×10-8) for glioblastoma and 25% (95% CI 17-32%, P=1.26×10-10) for non-GBM tumors . The currently identified GWAS risk loci explain approximately 6% of this common heritability , indicating that most heritable risk attributable to common genetic variants remains to be identified.

Synthesis

The genetic architecture of brain tumor susceptibility demonstrates substantial complexity with clear subtype specificity, ethnic heterogeneity, and pathway-specific effects that help explain apparent inconsistencies across studies.

Reconciling GBM vs. Non-GBM Differences

The distinct genetic susceptibility profiles for GBM and non-GBM gliomas represent one of the most consistent findings across studies. GBM-specific loci (EGFR, CDKN2B-AS1, RTEL1, HEATR3, JAK1) implicate pathways involved in cell proliferation, telomere maintenance, and cell cycle regulation . In contrast, non-GBM-specific loci (CCDC26, PHLDB1, LRIG1, near IDH1) show associations with molecular features characteristic of lower-grade gliomas, including IDH mutation . This genetic distinctiveness is consistent with different molecular profiles resulting from different etiological pathways , and studies that combine all glioma subtypes may obscure subtype-specific associations.

Explaining Ethnic Heterogeneity in DNA Repair Gene Associations

The striking ethnic differences in DNA repair gene associations reflect genuine biological variation rather than methodological inconsistencies. ERCC2 rs13181 shows risk effects in Caucasians but protective effects in Asians , while XRCC1 rs1799782 demonstrates strong risk effects specifically in Asians . These patterns likely reflect:

1. Different linkage disequilibrium structures across populations
2. Gene-environment interactions with population-specific exposures
3. Epistatic interactions with other population-specific genetic variants

The EGF +61G/A polymorphism provides a clear example: in Asians, the AA genotype increases risk (OR 1.63) , while in Caucasians it is protective (OR 0.66) . Studies failing to stratify by ethnicity would find null associations due to cancellation of opposing effects.

Age-Specific Associations and Secondary GBM

The age-specific associations at 8q24.21 (rs55705857) and 7p11.2 help explain heterogeneity in GBM genetic studies. The rs55705857 variant, which confers risk for IDH-

mutant glioma, shows significant association only in younger patients (18-53) . This corresponds to higher IDH1/2 mutation frequency in younger GBM cases (15% vs. 0.8% in those 64+) , consistent with a higher proportion of "secondary" GBM arising from lower-grade tumors in younger patients. Studies not stratifying by age would dilute this association, particularly in older cohorts where primary GBM predominates.

Sex-Specific Effects and Incidence Disparities

The identified sex-specific effects partially explain the approximately 50% higher glioma incidence in males . Male-specific associations at EGFR and female-specific associations at 3p21.31 and TERT suggest distinct biological pathways. However, variance explained by these sex-specific SNPs remains modest (1.4% overall) , indicating that most sex differences in incidence are not explained by identified genetic variants and may involve hormonal or other environmental factors interacting with genetic susceptibility.

Telomere Biology: A Central Mechanism

The convergence of evidence on telomere biology provides mechanistic insight into glioma susceptibility. Three major loci (TERT, TERC, RTEL1) influence telomere maintenance, with risk alleles generally associated with longer telomeres . The consistent association between longer telomeres and increased glioma risk supports a model where enhanced proliferative potential increases tumor risk. Importantly, RTEL1 associations appear partially independent of telomere length effects , suggesting additional mechanisms involving DNA repair and replication fork stability .

Low Common Heritability Explained

The heritability analysis estimating 25% attributable to common variants , with only 6% explained by known loci, indicates substantial remaining genetic architecture to be discovered. This includes:

1. Additional common variants with smaller effect sizes

2. Rare variants with larger effects (estimated 10% of childhood gliomas from rare germline mutations)
3. Gene-gene and gene-environment interactions not captured by additive models
4. Subtype-specific variants masked by combining heterogeneous tumor types

Immune-Mediated Susceptibility

The consistent inverse associations between autoimmune conditions and glioma risk , combined with enrichment of glioma risk variants in immune cell expression pathways , suggest that enhanced immune surveillance may protect against glioma development. The specific involvement of dendritic cells and NK cells in glioma predisposition identifies potential therapeutic targets and biomarkers for risk stratification.

Clinical Implications

Several findings have direct clinical relevance:

1. The distinct genetic architecture of GBM and non-GBM gliomas supports treating these as etiologically different diseases requiring different prevention and treatment strategies
2. Germline testing for high-penetrance variants (NF2, NF1, TP53) is warranted in specific clinical contexts, particularly pediatric patients
3. The identification of druggable pathways (JAK-STAT, EGFR, telomerase) through genetic studies provides rational targets for therapeutic development
4. Polygenic risk scores incorporating subtype-specific and sex-specific variants may improve risk stratification in clinical practice

DISCUSSION

This systematic review synthesizes two decades of evidence, revealing a complex and multifaceted genetic architecture underlying brain tumor susceptibility. The findings underscore

that brain tumors are not a monolithic entity but a collection of diseases with distinct etiological pathways influenced by a tapestry of genetic, demographic, and molecular factors.

Subtype-Specific Genetic Architecture: A Paradigm Shift

One of the most robust and clinically relevant findings is the fundamental genetic divergence between glioblastoma (GBM) and non-GBM gliomas. Large-scale GWAS meta-analyses have conclusively demonstrated that these subtypes harbor largely non-overlapping sets of susceptibility loci (Melin et al., 2017; Kinnersley et al., 2017). GBM-specific risk is strongly linked to loci involved in growth factor signaling (*EGFR* at 7p11.2) and telomere maintenance (*RTEL1* at 20q13.33), pathways central to the rapid proliferation and cellular immortality hallmark of this aggressive tumor (Walsh et al., 2014). In stark contrast, non-GBM gliomas, particularly those with IDH mutations, show stronger associations with loci like *CCDC26* (8q24.21) and near *IDH1* itself (2q33.3) (Eckel-Passow et al., 2020). This genetic dichotomy reinforces the biological distinction between primary *de novo* GBM and secondary GBM that progresses from lower-grade, often IDH-mutant, precursors. Consequently, future etiological studies and risk prediction models must treat these as separate entities to avoid diluting subtype-specific signals and to accurately reflect their different origins.

Ethnic Heterogeneity: Beyond Methodological Artifact

The review highlights striking ethnic disparities in the effect sizes and even directions of associations for several polymorphisms. The *EGF* +61G/A (rs4444903) variant, for instance, confers increased glioma risk in Asian populations but appears protective in Caucasians (Chen et al., 2014). Similarly, DNA repair gene polymorphisms like *XRCC1* rs1799782 show significant risk effects in Asian cohorts that are not replicated in European studies (Tavares et al., 2020). These patterns are unlikely to be mere artifacts of study design but reflect genuine biological diversity. They may arise from differences in linkage disequilibrium structures, leading to the studied SNP tagging different causal variants in different populations. More importantly, they may indicate

profound gene-environment or gene-gene (epistatic) interactions, where the genetic risk is modulated by population-specific lifestyle factors or co-inherited genetic backgrounds (Jacobs et al., 2012). This heterogeneity mandates that genetic risk profiles be calibrated for specific ethnic groups and cautions against the blanket application of findings from one population to another.

Demographic Modifiers: Sex and Age

Genetic susceptibility is further refined by demographic factors. Sex-specific genetic effects offer a partial explanation for the consistent male predominance in glioma incidence. Male-specific associations at the *EGFR* locus and female-specific loci at 3p21.31 suggest that hormonal milieu or sex-specific gene regulation may interact with genetic risk (Ostrom et al., 2018). Age-stratified analyses reveal that the strong association of the *CCDC26* variant (rs55705857) with lower-grade glioma risk is virtually confined to younger adults (aged 18-53) (Ostrom et al., 2018). This aligns with the observation that younger GBM patients have a much higher frequency of IDH mutations, a marker of secondary GBM. This suggests that genetic studies in older cohorts are predominantly capturing the genetics of primary GBM, while studies in younger adults reflect a mix that includes the genetics of lower-grade precursors.

Telomere Biology: A Central Unifying Mechanism

The convergence of multiple GWAS signals on telomere maintenance genes (*TERT*, *TERC*, *RTEL1*) provides a compelling mechanistic narrative (Walsh et al., 2014). Risk alleles at *TERT* and *TERC* are associated with longer leukocyte telomere length, supporting a model where longer telomeres grant cells a greater proliferative potential, increasing the probability of accumulating oncogenic mutations over a lifetime. Interestingly, *RTEL1* associations may be partially independent of telomere length, implicating additional roles in DNA replication fork stability and repair. This pathway highlights how germline genetics can establish a permissive cellular environment for tumorigenesis long before the acquisition of driver mutations.

The Immune Connection and Causal Insights

Mendelian randomization studies have transformed our understanding of risk factors by providing evidence for (or against) causality. The consistent inverse genetic correlations between glioma risk and autoimmune diseases like multiple sclerosis and ulcerative colitis suggest that a genetically determined robust immune system may enhance immunosurveillance against nascent glioma cells (Ostrom et al., 2019; Ostrom et al., 2021). Conversely, genetically predicted allergic disease appears to increase glioblastoma risk, pointing to a complex, subtype-specific role of immune dysregulation. These findings move beyond correlation to suggest shared biological pathways—such as those involving dendritic cell and natural killer cell function—that could be harnessed for immunotherapy or prevention.

The Heritability Gap and Future Directions

A critical synthesis from this review is the quantification of the "heritability gap." Genome-wide complex trait analysis estimates that approximately 25% of glioma risk is due to common genetic variants, yet the pooled GWAS-identified loci explain only about 6% of this (Kinnersley et al., 2015). This significant shortfall, the "missing heritability," points to several frontiers for discovery: 1) **Rare variants:** High-penetrance germline mutations in genes like *TP53*, *NF1/2*, and *DICER1* account for a minority of cases but are crucial in specific contexts (e.g., pediatric tumors, familial clusters) (Vuong et al., 2022; Foss-Skiftesvik et al., 2022). 2) **Gene-gene and gene-environment interactions:** The additive models used in GWAS may miss important synergistic effects. 3) **Non-coding and regulatory variation:** Integrative multi-omics studies using expression QTLs (eQTLs), splicing QTLs (sQTLs), and chromatin interaction data are beginning to pinpoint the target genes and regulatory mechanisms of non-coding risk loci, as seen with *CDKN2B-AS1* (Patro et al., 2021; Thornton et al., 2024). 4) **Diverse biobanks:** Expanding research beyond European-ancestry populations is essential to fully capture the genetic architecture and address health disparities.

Clinical Translation and Conclusion

The translational implications of this genetic knowledge are substantial. It argues for the integration of molecular subtype (IDH status, 1p/19q codeletion) into etiological research and clinical trial design. Germline genetic testing, particularly in pediatric and familial settings, is increasingly warranted (van den Broek et al., 2019). Furthermore, the identification of druggable pathways (e.g., JAK-STAT via *JAK1* associations, EGFR, telomerase) through genetic association provides a powerful rationale for developing targeted chemoprevention or therapies. Finally, the construction of refined polygenic risk scores that incorporate subtype-specific, sex-specific, and ancestry-specific variants holds promise for stratifying individuals in high-risk screening programs. In conclusion, the genetic landscape of brain tumors is one of remarkable complexity and specificity. Unraveling this landscape is key to transforming our approach from generic treatment to personalized prevention, precise diagnosis, and targeted intervention.

CONCLUSION AND RECOMMENDATIONS

Conclusion: This comprehensive systematic review firmly establishes that genetic factors play a critical and multifaceted role in the development of primary brain tumors. The evidence reveals a polygenic landscape marked by clear subtype specificity (e.g., GBM vs. non-GBM), significant ethnic heterogeneity, and modulation by age and sex. Core biological pathways, particularly telomere maintenance, DNA repair, growth factor signaling, and immune regulation, are recurrently implicated. While GWAS have successfully identified numerous common risk loci, they explain only a fraction of the estimated heritability, highlighting a substantial "missing heritability" gap. Mendelian randomization studies have provided valuable causal insights, linking immune traits and other factors to disease risk. The integration of this genetic knowledge is essential for advancing our understanding of brain tumor biology.

Recommendations: To build upon these findings and address existing gaps, the following actions are recommended:

1. **Prioritize Diverse and Large-Scale Genomics:** Future studies must actively recruit from underrepresented ethnic populations to ensure genetic risk profiles are globally applicable and to discover population-specific variants. Large, international consortia with deep phenotyping (including molecular subtypes like IDH status) are needed.

2. **Embrace Multi-Omics Integration:** Research should move beyond SNP associations to integrate genomic data with transcriptomic, epigenomic, and proteomic layers. This will help identify the functional genes, regulatory elements, and biological mechanisms behind GWAS signals, as pioneered by eQTL and sQTL studies (Patro et al., 2021).

3. **Investigate Interactions and Rare Variants:** Dedicated efforts are required to systematically explore gene-gene (epistasis) and gene-environment interactions. Simultaneously, whole-genome or whole-exome sequencing in familial and early-onset cases is crucial to catalog rare, high-penetrance variants.

4. **Accelerate Clinical Translation:** Develop and validate clinically useful polygenic risk scores that incorporate subtype and demographic information. Establish clear guidelines for germline genetic testing in brain tumor patients, especially children and those with a family history. Use genetic discoveries to repurpose or develop drugs targeting identified causal pathways (e.g., JAK-STAT inhibitors).

5. **Foster Interdisciplinary Collaboration:** Closing the loop from genetic discovery to clinical impact requires sustained collaboration between geneticists, bioinformaticians, neuro-oncologists, and public health researchers.

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