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Genetic epidemiology and risk factors for brain tumors

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ABSTRACT This report summarized current knowledge and findings relevant to environmental and genetic risk factors in brain tumors, with a particular focus on glioma. To date, the established risk factors for brain tumors are family history and ionizing radiation exposure; whereas there is an inverse association between tumors and other factors such as history of allergies, atopic conditions, chickenpox, and varicella zoster virus infection. To identify inherited genetic variants impacting susceptibility of brain tumors, large scale familial linkage-scan pedigree analysis, population-based candidate genes, and genome-wide association study were performed. More recently, next generation exome and whole genome sequencing studies were also conducted.

KEY WORDS epidemiology; brain tumor; glioma; ionizing radiation; polymorphism

脑肿瘤遗传流行病学及危险因素研究进展

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[摘要] 总结目前在脑肿瘤特别是胶质瘤领域关于其环境及遗传危险因素的主要认识及发现。脑肿瘤家族患病史及电离辐射暴露史为已明确的脑肿瘤危险因素；而其他因素如过敏史、特应性状态、水痘病史、水痘-带状疱疹病毒感染则为与脑肿瘤发病存在负性关系的潜在因素。此外，目前已有一些采用大规模家族连锁-扫描系谱分析、全基因组关联分析和采用下一代外显子及全外显子测序技术的研究，旨在进一步识别与脑肿瘤易感性相关的遗传变异。

[关键词] 流行病学；脑肿瘤；胶质瘤；电离辐射；多态性

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Brain and other nervous system cancers account for only 1%–4% of all new cancer cases and about 3% of cancer deaths[1]. The incidence of primary brain tumors varies significantly in country, race, and ethnicity. Generally, the highest incidence is recorded in European countries, and the lowest incidence is recorded in African countries (half that of Caucasians)[2]. According to the data of 2010 Central Brain Tumor Registry of the United States (CBTRUS, www.cbtrus.org)[2], the overall incidence rate for primary brain tumors among African Americans is 17.36 per 100 000, compare to Hispanics with 17.73 per 100 000, and Caucasians with 19.13 per 100 000. The incidence of high-grade gliomas in Tibetans is significantly lower than that in the Chinese Han population between 2008 and 2013[3].

Most of brain tumors are rapidly fatal, with an average 5-year survival rate of about 33%. Cause-specific mortality due to malignant brain tumors varies significantly by countries. Survival also varies depending on tumor grade across all glioma subtypes. Pilocytic astrocytoma (WHO grade I) is associated with the highest survival rate[2-4]. Glioblastoma (GBM) is associated with the poorest overall survival, with only 0.05%–4.7% of patients surviving 5 years after diagnosis. Other factors, i.e., age, extent of tumor resection, and Karnofsky performance status[4] are also significantly associated with survival after diagnosis for all gliomas, particularly for GBM[2].

1 Non-genetic risk factors

Compared with many other cancers, little is known about the risk factors for brain tumors. Identifying environmental factors, non-genetic biological factors, and investigations of their interactions are vitally important, as a substantial proportion of glioma risk may be attributable to such factors. Because these tumors tend to be rare and highly fatal, epidemiological studies often encounter methodological difficulties in patient recruitment and eligibility, as well as generalizability[5]. To validate traditional epidemiological or any environmental factors that have been associated with brain tumors with relative consistency, consortium studies and data pooling projects are of key importance.

Currently, the only established environmental risk factor for brain tumors is moderate- to high-dose ionizing radiation exposure[6-7]. Preliminary evidence suggests that DNA repair ability and susceptibility to cancer may be related to differences in γ-radiation sensitivity[8]. One source of radiation exposure is through to be from therapeutic or prophylactic radiation to the brain tumors, which tends to result in high-dose exposures (≥5 Gy)[9-10]. Another source of exposure to radiation involves treatment for tinea capitis or hemangiomas, which tends to result in a moderate dose of exposure (0.15–5 Gy)[9]. Furthermore, some studies[11-12] suggest that children who have low-dose (typically <10 mGy) CT scans and diagnostic X-rays may increase cancer risk, including brain cancer. Several studies have also examined the effects of occupational exposures to radiation. Airline pilots have not been shown to have increased brain tumor risk[13-14]. A nationwide prospective cohort study[15] on 90 957 radiologic technologists, who reported working with fluoroscopically guided interventional procedures, has showed an 2-fold increased risk of brain cancer mortality.

A positive history of allergies and asthma has consistently been associated with a reduced risk of glioma across many epidemiological studies in the past 3 decades. Allergies, atopic conditions (i.e., asthma, eczema), and higher levels of immunoglobulin E are associated with a lower risk of glioma, and the magnitudes of reduction generally range from 20% to 40% in risk[16-19]. Future studies will be needed to determine the biological mechanism underlying the protective effect of allergies against gliomas and the immunological factors driving this association. This may lead to new avenues for the development of immunotherapeutic or immuno-preventive purposes.

Of the many viruses suspected to be involved in glioma susceptibility, varicella zoster virus (VZV) is the only virus consistently reported to have an inverse association with glioma[20]. Using data from the Glioma International Case-Control Study (one of the largest studies of glioma to date), Amirian et al[21] recently found that a positive self-reported history of chickenpox is associated with a 21% lower glioma risk, controlling for age and sex. A cohort study has also found similar inverse associations between chickenpox or VZV infection and glioma risk[22].

In addition, many previous studies have investigated the role of chemical exposures (e.g., pesticides, heavy metals, and nitroso compounds), alcohol and/or tobacco,

dietary, medications (e.g., vitamins C and E, non-steroidal anti-inflammatory drugs, and antihistamines), female hormone-related/reproductive factors (e.g., use of hormone replacement therapy and oral contraceptives), physical factors (e.g., electromagnetic fields, including those produced by cell phones, head trauma, and seizures), infectious agents (e.g., herpesviruses, retroviruses, polyomaviruses, and adenoviruses), and energy balance-related factors (e.g., body mass index, higher birth weight, and taller height), but none of these factors has been definitively established to be involved in risk of brain tumors (Table 1). One of the challenges faced by analytic epidemiology studies on brain tumors is related to identifying a homogenous set of tumors, which is an important aspect of study design given that different tumor subtypes could have divergent etiologies. Additional challenges are use of appropriate control groups in case-control studies, consistencies in histological classifications, accurate exposure assessment in retrospective studies, and defining the latency periods between exposure and outcome.

Table 1 Summary of the risk factors for brain tumors

Risk factors for brain tumors	Evidence
Established factors	
Moderate- to high-dose ionizing radiation exposure	Risk
History of allergies and atopic conditions (asthma and eczema)	Protection
Varicella zoster virus and chickenpox	Protection
Non-established factors	
Chemical exposures (pesticides, heavy metals, and nitroso compounds)	Disagreement
Alcohol and tobacco	Disagreement
Medications (vitamins C and E, non-steroidal anti-inflammatory drugs, and antihistamines)	Disagreement
Hormone-related/reproductive factors (use of hormone replacement therapy and oral contraceptives)	Disagreement
Physical factors (cell phones, head trauma, and seizures)	Disagreement
Infectious agents (herpesviruses, retroviruses, polyomaviruses, and adenoviruses)	Disagreement
Energy balance-related factors (body mass index, birth weight, and height)	Disagreement

2 Genetic risk factors

Understanding the genetic factors underlying the development of brain tumors is important to elucidate the etiology of the disease. Although it has long been recognized that brain tumors run strongly in families, the specific genes and inherited genetic variations (germline polymorphisms) that are responsible for enhanced risk are just starting to be revealed. The key reasons that this field of study has been, and will continue to be, of high relevance are as follows: the detection of susceptibility genes fosters a more complete understanding of the mechanisms of tumor biology; susceptibility genes may confer potential therapeutic targets for medical intervention; and the ability to identify individuals at increased risk is of immediate clinical relevance in terms of primary and secondary interventions and genetic counseling.

2.1 Linkage-scan pedigree analysis

Approximately 5% of patients with brain tumors also have a first-degree family member diagnosed with a brain tumor[23]. Several heritable syndromes are associated with a higher incidence of brain tumors, including Li-Fraumeni, neurofibromatosis, tuberous sclerosis, nevoid basal cell carcinoma syndrome, familial polyposis, and von Hippel-Lindau. Family studies have often been restricted by their relatively small size and lower marker density. However, despite their relatively low power, results of pedigree analyses can provide strong and persuasive evidence of genetic linkage effects because they are based on genetic transmission of disease alleles within a family and thus do not make the same population assumptions as association studies. The Gliogene International Consortium used a genome-wide approach to conduct non-parametric[24] and parametric linkage[25] scans for US families and detected a major disease locus on chromosome 17q12-

21.32 and another region with evidence of suggestive linkage at 18q23. The identification of an association peak at 17q12-21.32 is particularly interesting because it is present in 35% of Gliogene families[24]. Thus, these two regions may contain important genes that contribute to gliomagenesis[26]. Although the evidence of familial risks in brain tumors is largely positive with some exceptions, data on childhood brain tumors have not generally supported strong familial effects.

2.2 Candidate gene and pathway association analysis

The majority of the candidate gene-association studies[27-29] for glioma susceptibility have focused largely on 4 key pathways: DNA repair (particularly, double-strand break repair), cell cycle, inflammation (allergies and infections), and metabolism. An updated collection of these studies is available at the Genetic Association Database online (http://geneticassociationdb.nih.gov/). Although somewhat interesting results have been reported, many of these candidate gene studies are either preliminary or controversial. Only a few genes and single nucleotide polymorphisms (SNPs) have been consistently associated with glioma: DNA repair genes PRKDC (protein kinase, DNA-activated, catalytic polypeptide) p.G6721T, XRCC1 (X-ray repair cross complementing 1) p.W399R, PARP1 (poly ADP-ribose polymerase 1) p.A762V, MGMT (O^6-methylguanine-DNA methyltransferase) p.F84L, ERCC1 (excision repair cross-complementing 1, endonuclease non-catalytic subunit) p.A8092C, and ERCC2 (excision repair cross-complementing 2, TFIIH core complex helicase subunit)p.Q751K; cell cycle gene EGF (epidermal growth factor) +61 A/G; and inflammation gene IL13 (interleukin 13) p.R110G (Table 2).

Table 2 Selected glioma susceptibility genes and SNPs observed in at least 2 candidate association studies

Pathways	Genes	Associated SNPs
Double strand break DNA repair	PRKDC	G6721T(rs7003908)
Base excision DNA repair	XRCC1	W399R(rs25487)
	PARP1	A762V(rs1136410)
Nucleotide excision DNA repair	ERCC1	A8092C(rs3212981)
	ERCC2	Q751K(rs13181)
DNA direct reversal of damage	MGMT	F84L(rs12917)
Cell cycle	EGF	+61 A/G(rs4444903)
Inflammation	IL13	R110G(rs20541)

2.3 Genome-wide association analysis

In the post-genome sequencing era, over 10 million SNPs are now documented, coupled with the development of highly efficient analytical platforms and techniques are allowing genome-wide association analysis (GWAS) to be conducted in a cost-effective manner (Table 3). By adopting this approach, important progress has been made to understand host susceptibility to brain tumor. Using GWAS, 5 risk loci for glioma have been identified in the first glioma GWAS including 1 878 glioma patients and 3 670 controls, and validated in 2 545 glioma patients and 2 953 controls: 5p15.33 TERT (telomerase reverse transcriptase), 8q24.21 CCDC26 (coiled-coil domain containing 26), 9p21.3 CDKN2A-CDKN2B (cyclin dependent kinase inhibitor), 20q13.33 RTEL1 (regulator of telomere elongation helicase 1), and 11q23.3 PHLDB1 (pleckstrin homology like domain family B member 1)[30]. Wrensch et al[31] contributed additional evidence implicating the CDKN2A-CDKN2B, RTEL1, and TERT variants in high-grade gliomas. Another GWAS identified 2 additional genetic variants[32]: 7p11.2 EGFR (epidermal growth factor receptor) and 7q36.1 XRCC2 (X-ray repair cross complementing 2). Recently, a Meta-analysis of existing GWAS and 2 new GWAS, with total 12 496 glioma cases and 18 190 controls, has been performed by the Glioma International Case Control Consortium[33]. This study has been identified 5 new loci for GBM at 1p31.3 RAVER2 (ribonucleoprotein, PTB binding 2), 11q14.1 RPS28P7 (ribosomal protein S28 pseudogene 7), 16p13.3 MPG (N-methylpurine DNA glycosylase), 16q12.1 HEATR3 (HEAT Repeat Containing 3), and 22q13.1 SLC16A8

(solute carrier family 16 member 8), as well as 8 loci for non-GBM tumors at 1q32.1 MDM4 (mouse double minute 4, human homolog; P53-binding protein), 1q44 AKT3 (AKT serine/threonine kinase 3), 2q33.3 IDH1 (isocitrate dehydrogenase 1, cytosolic), 3p14.1 LRIG1 (leucine rich repeats and immunoglobulin like domains 1), 10q24.33 OBFC1 (oligonucleotide/oligosaccharide-binding fold-containing protein 1), 11q21 MAML2 (mastermind like transcriptional coactivator 2), 14q12 AKAP6 (A-kinase anchoring protein 6), and 16p13.3 LMF1 (lipase maturation factor 1). These data substantiate that genetic susceptibility to GBM and non-GBM tumors are highly distinct, which likely reflects different etiologies. In addition, inherited variants of LIG4 (DNA ligase 4), BTBD2 (BTB domain containing 2), HMGA2 (high mobility group AT-hook 2), and RTEL1 genes which involved in the double-strand break repair pathway are also associated with GBM survival[34] and neurocognitive function[35].

Table 3 Summary of the susceptibility genes and SNPs in glioma GWAS

Chromosome	Genes	SNP ID and genic location*
1p31.3	RAVER2	rs12752552*
1q32.1	MDM4	rs4252707*
1q44	AKT3	rs12076373*
2q33.3	IDH1	rs7572263*
3p14.1	LRIG1	rs11706832*
3q26.2	TERC	rs1920116*, rs3772190*
5p15.33	TERT	rs72709458*, rs2736100*, rs2853676*, rs10069690*
5q14.1	SSBP2	rs7732320*
7p11.2	EGFR	rs2252586 (intergenic), rs75061358 (intergenic)
7p11.2	EGFR	rs723527*, rs11979158*, rs59060240*
8q24.21	CCDC26	rs891835*, rs4295627*, rs55705857*
9p21.3	CDKN2A/2B	rs634537*, rs4977756*, rs2157719*, rs145929329*, rs1412829*
10q24.2	HPSE2	rs12780046*
10q24.33	OBFC1	rs11598018*
10q25.2	VTI1A	rs11599775*
11q14.1	RPS28P7	rs11233250*
11q21	MAML2	rs7107785*
11q23.2	ZBTB16	rs648044*
11q23.3	PHLDB1	rs498872 (5' UTR)
11q23.3	PHLDB1	rs12803321*
12q21.2	RN7SL734P	rs1275600*, rs12230172*
12q23.3	POLR3B	rs3851634*
12q24.33	VTI1A	rs111696067*
14q12	AKAP6	rs10131032*
15q24.2	ETFA	rs77633900*, rs1801591 (missense)
16p13.3	MPG	rs2562152*
16p13.3	LMF1	rs3751667 (synonymous)
16q12.1	HEATR3	rs10852606*
17p13.1	TP53	rs78378222 (3' UTR), rs35850753 (5' UTR)
17p13.1	POLR2A	rs8753 (non-coding)
20q13.33	RTEL1	rs2297440*, rs6010620*, rs2236507*
20q13.33	RTEL1	rs4809324 (non-coding), rs6062302 (synonymous)
22q13.1	SLC16A8	rs2235573 (synonymous)

*Intronic variants

2.4 Exome sequencing

Rare germline variants (minor allele frequencies < 1%) with modest- to high-effect sizes might play a vital role in identifying the etiology of complex diseases and help account for missing heritability that remains unexplained by common variants. Next-generation exome sequencing focuses on the protein-coding and regulatory regions of the genome and seeks to identify mutations that affect protein translation and expression. Exome sequencing is also expected to refine GWAS loci and discover new variants. Using data from targeted sequencing to examine familial glioma candidate genes and variants on the chromosome 17q linkage region[24], the rare variants in MYO19 (myosin XIX), KIF18B (kinesin family member 18B), SPAG9 (sperm associated antigen 9), and RUNDC1 (RUN domain containing 1) were identified as potentially candidates for disease risk[26]. Furthermore, using whole exome sequencing of 90 individuals from 55 families[36], candidate mutations, p.G95C and p.E450X, in POT1(protection of telomeres 1) which is a member of the telomere Shelterin complex, has been identified. Another mutation p.D617E, in POT1, which is also predicted to disrupt TPP1(tripeptidyl peptidase 1) binding, has been verified in a separate cohort of 264 individuals from 246 families[36]. Interestingly, all families with POT1 mutations had affected members with oligodendrogliomas.

2.5 Glioma genetic association studies in Chinese Han population

The ethnic differences in brain tumor incidence and mortality exist and are also probably the result of genetic and epidemiological risk factors. To date, most of the study population in the glioma association studies were primarily of European origin, very few have explored in the African Americans and/or Hispanics. However, in the Chinese Han population, many candidate gene or pathway-based association studies have also been conducted, and identified glioma susceptibility variants in DNA repair pathway genes (i.e., ERCC1, ERCC2, ATM, RAD54L, NBS1, MRE11, XRCC1, XRCC3, LIG4, XRCC4, XRCC5, XRCC6, XRCC7, and H2AFX)[37-46], vascular endothelial growth factor genes (i.e., EGF, VEGFA, VEGFR2, CCND1, and EFEMP1)[47-54], cytokine genes (i.e., IL10, IL13, IL4, and IL4R)[55-56], and others (i.e., BCL2, SPP1, STAT5, MMP3, CTLA4, RBBP6, APE1, and SLC2A4RG)[57-65]. An protective effect of the A allele of rs730437 in EGFR on glioma risk has been found in Chinese glioma patients[66-67], in contrast to its previous-proven risk-increasing effects in European patients[68]. These differences in disease susceptibility could be contributed by variant frequencies in individuals from ethnicvariation. Of the known glioma GWAS susceptibility variants identified in European populations, variants in 5p15.33 TERT, 8q24.21 CCDC26, 20q13.33 RTEL1, and 11q23.3 PHLDB1 are also significantly associated with glioma risk in the Chinese Han population[45, 69-73]. Future epidemiology analysis among different ethnic groups could lead to further understanding of glioma pathogenesis and may be useful to targeted interventions.

3 Future directions

Discovered germline variants may not only exert their effects through gene regulation, but also other molecular phenotypes such as protein expression, protein state, metabolite levels, and epigenetic marks. Accordingly, deep molecular profiling of human brain tissues will be needed to comprehend the molecular impact of both inherited and somatic variants on brain tumors. Recently, mouse models for preclinical testing of therapeutics and other impactful research purposes have developed substantially[74-75]. In particular, the use of CRISPR (clustered regularly interspaced short palindromic repeats) technology has revolutionized the ability to conduct functional studies of oncogenes and other targets in vivo. The CRISPR technology can help us uncover the role of the interest genes in the biological mechanisms that lead to cancer development. For example, Zuckermann et al[76] used CRISPR/Cas9-mediated somatic gene disruption to delete Ptch1 and a set of genes (Trp53, Pten, Nf1) in the mouse brain, resulting in the development of medulloblastoma and GBM, respectively. Such studies can be used to assess whether the genetic markers identified through epidemiologic studies are truly the potential causative mutations, or whether they are simply a marker of another nearby mutation that may be correlated with the one observed.

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