The molecular epidemiology of gliomas in adults

MARGARET WRENCH, PH.D., JAMES L. FISHER, PH.D., JUDITH A. SCHWARTZBAUM, PH.D., MELISSA BONDY, PH.D., MITCHEL BERGER, M.D., AND KENNETH D. ALDAPE, M.D.

Department of Neurological Surgery, University of California, San Francisco, California; The Arthur G. James Cancer Hospital and Richard J. Solove Research Institute; The Ohio State University Comprehensive Cancer Center; Division of Epidemiology and Biometrics, School of Public Health, The Ohio State University, Columbus, Ohio; Institute of Environmental Medicine, Karolinska Institute, Stockholm, Sweden; Departments of Epidemiology and Pathology and Brain Tumor Center, The University of Texas M. D. Anderson Cancer Center, Houston, Texas

In this paper the authors highlight recent findings from molecular epidemiology studies of glioma origin and prognosis and suggest promising paths for future research. The reasons for variation in glioma incidence according to time period of diagnosis, sex, age, ancestry and ethnicity, and geography are poorly understood, as are factors that affect prognosis. High-dose therapeutic ionizing irradiation and rare mutations in highly penetrant genes associated with certain rare syndromes—the only two established causes of glioma—can be called upon to explain few cases. Both familial aggregation of gliomas and the inverse association of allergies and immune-related conditions with gliomas have been shown consistently, but the explanations for these associations are inadequately developed or unknown. Several biomarkers do predict prognosis, but only evaluation of loss of 1p and 19q in oligodendrogial tumors are incorporated in clinical practice. Ongoing research focuses on classifying homogeneous groups of tumors on the basis of molecular markers and identifying inherited polymorphisms that may influence survival or risk. Because most cases of glioma have yet to furnish either an environmental or a genetic explanation, the greatest potential for discovery may lie in genomic studies in conjunction with continued evaluation of environmental and developmental factors. Large sample sizes and multidisciplinary teams with expertise in neuropathology, genetics, epidemiology, functional genomics, bioinformatics, biostatistics, immunology, and neurooncology are required for these studies to permit exploration of potentially relevant pathways and modifying effects of other genes or exposures, and to avoid false-positive findings. Improving survival rates for patients harboring astrocytic tumors will probably require many randomized clinical trials of novel treatment strategies.

Key Words • glioma • polymorphism • epidemiology • tumor marker • survival • prognosis

Molecular epidemiology integrates molecular technologies and ideas into epidemiological studies of disease origins and outcomes. The translational goals of such research are to understand a disease sufficiently to enable the development of strategies to reduce the patient population burden. With respect to glioma origin and survival rates for adults, approaches based on molecular epidemiology have been used to classify glial tumors into more homogeneous categories, to study the roles of common genetic polymorphisms, and to identify biomarkers related to developmental or environmental risk factors for gliomas. Because there have been several recent reviews of brain tumor epidemiology and pathogenesis, we refer interested readers to these papers for details.8,14,74,78,115,123,183 The purpose here is to provide the context for molecular epidemiology studies of gliomas, to highlight recent findings, and to suggest promising paths for future research.

Abbreviations used in this paper: CI = confidence interval; CYP = cytochrome P-450; EGFR = epidermal growth factor receptor; GBM = glioblastoma multiforme; GST = glutathione S-transferase; IL = interleukin; OR = odds ratio.

Impact and General Epidemiology of Gliomas

The term “glioma” refers to tumors thought to be of glial cell origin and includes astrocytic tumors (World Health Organization astrocytoma classification of Grades I, II [astrocytoma], III [anaplastic astrocytoma], and IV [GBM]), oligodendrogliomas, ependymomas, and mixed gliomas.28,88,99 Approximately 13,000 deaths and 18,000 new cases of primary malignant brain and central nervous system tumors occur annually in the US; approximately 77% of these are brain gliomas.28 Primary brain and central nervous system tumors rank first among cancer types for the average years of life lost, with an average of 20.1 years (compared, for example, with 6.1 years for prostate cancer and 11.8 years for lung cancer).21 Survival from GBM, the most common form of glioma in adults, is poor; with median survival time approximately 3.5 months for patients 65 years or older at diagnosis and only 10 months for those under 65 years, according to data collected by the Surveillance Epidemiology and End Results Program.89 Approximately 2% of patients 65 years of age or older and only 30% of those young-
er than 45 years at GBM diagnosis survive for 2 years.\textsuperscript{28} Furthermore, although survival rates for individuals with GBM have shown no notable improvements in population statistics for more than 30 years,\textsuperscript{28} recent clinical trial data on the use of combined radiotherapy and temozolomide found a median survival period of 14.6 months compared with 12 months for patients treated with radiotherapy alone.\textsuperscript{154}

**GENERAL MOLECULAR PATHOLOGICAL NATURE OF GLIOMAS**

**Commonly Altered Chromosomal Regions**

Classic cytogenetic and array-based comparative genomic hybridization studies of gliomas have identified copy number changes (deletions, amplifications, and gains) in several regions; deletions and loss of heterozygosity in tumors may indicate genes involved in tumor suppression, whereas amplifications and gains may point to genes involved in tumor initiation or progression (for example, oncogenes). The more regularly observed of these changes, which may vary by histological type, as well as some candidate genes in the regions include gains and deletions in 1p (1p36.31-pter, 1p36.22-p36.31, and p34.2-p36.1), gains in 1q32 (RIPK5, MDM4, PIK3C2B, and others), deletion of 4q (NEK1 and NIMA), amplifications and gains in chromosome 7 (7p11.2-p12, EGFR), deletions in chromosome 9 (9p21-p24, CDKN2), deletions in chromosome 10 (10q23, PTEN; 10q25-q26, MGMT), deletions in chromosome 11 (11p [between CDKN1C and RASA2]), amplifications of 12 (12q13.3-q15, MDM2, CDK4, and many others), loss of 13 (13p11-p13 and 13q14-q34, RB1), loss of 19 (19q13, GLTSCR1, GLTSCR2, LGi1, PSCD2, and numerous others), loss of 22 (the 22q11.21-12.2 region has 28 genes including INII, known for its involvement in rhabdoid tumors, and q13.1-13.3). These issues are reviewed by Ichimura, et al.,\textsuperscript{74} and many others.\textsuperscript{45,49,60,69,77,87,118,126,130,151,153,155,156} This brief summary demonstrates that although several well-known tumor suppressor genes and oncogenes occur in these regions, many genes in the regions have yet to be identified for their specific relationship to glioma genesis.

**Dysregulated Pathways in Astrocytic Gliomas**

Classic molecular and cytogenetic studies of tumors as well as the newer array-based assays of comparative genomic hybridization and RNA expression indicate substantial heterogeneity of genes and gene expression within and between histological grades of astrocytic tumors and between different histological types of gliomas.\textsuperscript{51,74,89,94,113,114,128} It has become increasingly apparent that such heterogeneity at the cellular level reflects the action of different causal mechanisms in the pathogenesis of the disease. Because astrocytic gliomas compose more than 70% of all adult gliomas, we emphasize pathways known to be important for these tumors and do not provide a comprehensive review here of this rapidly expanding area of research. The phenotype called GBM arises from dysregulation of several different pathways. Dysregulation can occur from a variety of genetic and epigenetic mechanisms, including gene mutation, amplification, deletion, methylation or demethyla-

**Molecular Pathways to GBM**

Progress has been made with respect to elucidating the genetic pathways that lead to GBMs. It is now believed that these tumors arise by two pathways that can be defined in clinical terms: one pathway results from tumor progression from lower-grade astrocytomas ("secondary" GBM) and a second pathway has no clinically evident precursor ("primary" or "de novo" GBM). Interestingly, examination of two molecular aberrations, TP53 mutation and EGFR amplification, has led to their correlation with the type of GBM defined on a clinical basis.\textsuperscript{94,164} Specifically, tumors with TP53 mutations are more likely to be secondary GBMs, arising from lower grade precursors, whereas a de novo GBM is more likely to harbor EGFR amplification. Although this distinction is not absolute and has recently been called into question,\textsuperscript{116} it raises the possibility that distinct subtypes of GBM may be similar histologically yet display clinical differences, specifically in response to therapeutic agents. Molecular subtyping is currently not routine but is likely to be of use in the future as an adjunct to histological analysis in the classification of these tumors.

**Population Studies of Tumor Markers in Astrocytic Gliomas**

To date only two studies have presented data on genetic and molecular tumor markers for relatively large numbers of population-based glioma cases.\textsuperscript{114,177} Although in each study five or six tumor markers were assessed, only two (EGFR amplification and TP53 mutation) were measured in both studies. Interestingly, the percentage of GBMs with EGFR amplification was identical in the two studies (36% of 371 de novo GBMs from Zurich and 36% of 386 GBMs from the San Francisco Bay area). The percentage of tumors with a TP53 mutation varied from 28% of 386 GBMs from Zurich to only 15% of 409 GBMs from San Francisco; percentages in clinical series have ranged from 20 to 30%.\textsuperscript{41} Despite some inconsistencies, these findings support the hypothesis, proposed in smaller clinical series, that astrocytic tumors may arise through different pathways and may reflect the action of different causal mechanisms. To summarize current findings for astrocytic tumors, TP53 tumor mutations are associated with a younger age at diagnosis and are more common in lower-grade tumors and in GBMs arising from them;\textsuperscript{42,89,114,127,177} TP53 tumor mutations are more common in non-Caucasians, whereas tumors overexpressing EGFR or containing p16 deletions are more common in Caucasians;\textsuperscript{106,177} MGMT 84Phe carriers are overrepresented among GBM cases in which tumors do not overexpress TP53 protein;\textsuperscript{177} and the GSTT1 constitutive deletion is more common among GBM cases in which the tumor displays the TP53 mutation.\textsuperscript{181}
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**TABLE 1**
Pathways dysregulated in GBM and other gliomas*

<table>
<thead>
<tr>
<th>Important Pathways</th>
<th>Pathway Functions and Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rb/p16/p15/CDK4/4i</td>
<td>CyclinD</td>
</tr>
<tr>
<td>TP53/MDM2/p14ARF</td>
<td>cell cycle arrest; apoptosis; dysregulation enhances cell proliferation, which combined w/ apoptotic failure leads to genomic instability</td>
</tr>
<tr>
<td>EGF/EGFR/PTDF/AlphdR</td>
<td>growth signaling stimulates cell proliferation, focal adhesion, MAPK (mitogen activated protein kinase) signaling, calcium signaling, actin cytoskeleton regulation, &amp; cytokine–cytokine receptor interactions</td>
</tr>
<tr>
<td>Ras/Raf/MAPK</td>
<td>pleiotropic effectors of cell physiology involved in gene expression, cell cycle, apoptosis, cell differentiation, &amp; cell migration</td>
</tr>
<tr>
<td>PI3-kinase/AKT</td>
<td>pleiotropic effectors preventing apoptosis &amp; influencing focal adhesion, MAPK signaling, tight junction, &amp; Toll-like receptor signaling</td>
</tr>
<tr>
<td>WNT signaling</td>
<td>cell cycle control, TGF-β; other components of WNT signaling affect focal adhesion, cytoskeletal change, &amp; gene transcription</td>
</tr>
<tr>
<td>HIF1-α/VEGF</td>
<td>response to hypoxia/angiogenesis pleiotropic effector involved in focal adhesion, phosphatidylinositol signaling system (suppresses PI3-kinase/AKT activation), tight junction</td>
</tr>
</tbody>
</table>


**SURVIVAL RATES AND PROGNOSIS FOR PATIENTS WITH GLIOMAS**

Information on survival rates and prognosis for patients with gliomas comes from clinical trials and population registry data. Studies from the Radiation Therapy Oncology Group and other clinical trial groups provide useful information on prognostic factors from cases whose pathological features have been centrally reviewed and for patients who qualify for and are treated in clinical trials. Because the majority of patients do not enter clinical trials, however, the results might not be applicable to or representative of the general population of patients with gliomas. Survival rate estimates based on population registry data can represent the full spectrum of patients in whom gliomas are diagnosed, yet pathological diagnoses are subject to considerable variability depending on numerous factors, including the pathologist’s neuropathological training and the time and place the diagnosis was made.55,61 Also, population registries do not generally have treatment data as extensive as that available from clinical trials.

Histological type and grade of tumor, patient age, extent of lesion resection, tumor location, whether the patient undergoes radiation therapy, and some chemotherapy protocols have been consistently and convincingly linked to survival in both population registry and clinical trial data.29,36,38,39,66,93,96,141,142 The Karnofsky Performance Scale score at diagnosis and other measures of mental and physical functionality also predict survival for patients with GBMs and anaplastic astrocytomas enrolled in the Radiation Therapy Oncology Group and other multiinstitutional clinical trials.36,93,142

In addition to these factors, investigators are currently trying to identify and understand tumor markers or patient characteristics that might influence survival or response to treatment.10,25,51,53,92,97,11,137,125,137,144,146,158,170,189 Specific examples are presented later in this paper. A key unsolved problem in neuro-oncology is the strong and consistent inverse relationship of age to survival. The reasons, whether they pertain to properties related to the tumor or the host, are not well understood. The response of tumors to radiation has been reported to be poorer in older patients.8 In this regard, one contributing factor may be related to different frequencies of molecular or chromosomal aberrations among tumors in older patients compared with those in younger patients (a topic that will be discussed subsequently). One difficulty in identifying prognostic factors in rapidly fatal gliomas such as GBMs may be related to the narrow range of survival time experienced by the vast majority of patients. One method to address this limitation is to compare tumors from rare long-term survivors with those from typical GBM survivors. Studies performed at the University of Texas M. D. Anderson Cancer Center, using both a candidate gene approach and a genome-wide screen,22 have indicated that differences exist between tumors obtained in long-term survivors and those obtained from typical GBM survivors.22 Although such studies may not be as easily extended to clinical use as prognostic markers, they point to aberrations that may be responsible for the nearly uniformly poor prognosis for patients with GBM.

**Studies of Tumor Markers in Relation to Survival**

Combined losses of 1p and 19q in oligodendroglial tumors are well-established favorable prognostic indicators.25,49,50,61,70,76,87,148,149,161 In astrocytic tumors, amplification/overexpression of EGFR is more common in older patients, especially those with anaplastic astrocytoma;72 this amplification/overexpression may also contribute to resistance to therapeutic modalities.6,139 Although EGFR amplification is more common in tumors from older individuals, it is not exclusive to that age group and may be associated with poor survival rates in younger (< 55–60 years of age) adults with GBM.146,150 A subset of tumors with EGFR amplification demonstrates an additional change in the EGFRI gene resulting from an internal rearrangement called EGFRIVIII. Although the results of large studies have yet to be reported, the presence of the EGFRIVIII allele may also be a negative prognostic factor.48,64 Data from a recent large prospective trial of patients with newly diagnosed GBMs have indicated that methylation of the MGMT promoter in GBM tumor samples was a marker of improved outcome, as measured by the 2-year survival rate.72 Interestingly, MGMT methylation appeared to be much more strongly associated with survival among patients who received frontline temozolomide than among those who did not.63 raising the possibility that MGMT methylation may be a predictive marker of response to this alkylating agent.
Insights From Expression Array Studies of Gliomas

In two recent studies the investigators assessed the prognosis for patients with gliomas from expression profiles alone or in conjunction with comparative genomic hybridization. Although some a priori candidate genes were validated, it was important that many new genes whose expression had not been previously linked to patients surviving gliomas were also identified, and abnormal expression in certain classes of genes predicted survival. For example, best, intermediate, and worst survival times were associated with the abnormal expression of neurogenesis genes, cell proliferation and mitosis genes, and extracellular and extracellular matrix genes, respectively. Other important findings include the following: 1) loss of chromosome 10 was accompanied by gene expression changes across the genome; and 2) the copy number loss of chromosome 10 and gains of chromosomes 7, 19, and 20 were highly correlated with one another. These findings, although compelling, are nevertheless preliminary because of the relatively small sample sizes typical of expression array studies. Candidate markers identified in such genome-wide screens, however, represent promising leads for possible validation in larger studies. A recent array study of oligodendroglioma and oligoastrocytoma found that a tumor gain of 8q may be a negative prognostic factor.

Constitutive Genetic Influences on Prognosis and Survival for Patients With Gliomas

It is being increasingly demonstrated that common gene polymorphisms influence response to cancer therapies or otherwise influence prognosis and survival (recent reviews on this topic include papers by Loktionov and Nagasubramanian, et al.). Survival after a diagnosis of glioma has been associated with polymorphisms in EGF, GSTP1, and GSTM1; HLA A*32 and B*55; and GLTSCR1 S397S and ERCC2 D711D. Because none of these findings has yet been replicated, cautious interpretation is advised. Potentially relevant associations between polymorphisms in genes and treatment response or survival for other cancer sites include the following: IL6 and aggressive breast cancer and ovarian cancer, ATM and radiosensitivity of breast cancer patients, TGFBI and breast cancer survival, TNF and myeloma relapse, GSTP1 and myeloma outcomes, MDRI and acute leukemia survival, FGFR4 and soft-tissue sarcoma survival, TYMS and colorectal cancer survival, CDKN2A and bladder cancer survival, and TP53 and lung cancer prognosis. One proposed mechanism is that TP53 variant alters function and the response of tumor cells to chemotherapeutic agents. The limited studies that have been performed to date have provided several potentially fruitful areas of discovery regarding genetic variation in relation to survival rates for patients with gliomas (for example, signaling pathways for growth factors, cell cycle regulators, modifiers of drug metabolism, and radiotherapy and the immune response).

ENVIRONMENTAL, DEVELOPMENTAL, AND GENETIC RISK FACTORS FOR GLIOMAS

The only exogenous environmental cause of gliomas that has been unequivocally established is high-dose therapeutic radiation; high-dose chemotherapy for other cancers is a strong possibility as well. Genetic factors influence risk from these exposures; Relling, et al. showed that among children treated with cranial radiotherapy and intensive antimetabolite therapy for acute lymphocytic leukemia, those with germline polymorphisms leading to low or absent thiopurine methyltransferase activity were significantly more likely than those without such polymorphisms to develop brain cancer.

Although abundant data obtained in animal and other studies support the biological plausibility of neurocarcinogenicity of endogenous and exogenous chemicals (for example, N-nitroso compounds, reactive oxygen and nitrogen species, several industrially used chemicals, and polycyclic aromatic hydrocarbons) to which people are exposed through their essential cellular metabolism, diet, occupation, and personal habits, inconsistent or often null findings from human studies result from a variety of issues. These include small study sample sizes, chance reporting of false-positive results, imprecise exposure measures (from proxy reporting and exposure history recall issues), inherited or developmental variation in metabolic and repair pathways, unaccounted for protective exposures, differential diffusion of chemicals across the blood–brain barrier, differentially expressed metabolic and repair pathways in the brain, and disease heterogeneity. Progress has been made in understanding environmental contributors to other cancers by joint consideration of inherited variation in detoxification, metabolism, or repair and histological or molecular tumor subtypes, such as TP53 mutations. Two classic examples include the demonstration that specific TP53 mutations in hepatocellular carcinoma occurred exclusively in carriers of variants in epoxide hydrolase and glutathione transferase mu and the finding that TP53 mutations in patients with lung cancer were more common in heavy smokers compared with non-smokers and that homozygous carriers of the glutathione transferase mu deletion were more likely to have transversion mutations in TP53. More recent examples have shown interactions between a vitamin D receptor polymorphism and dietary calcium and vitamin D intake in evaluating the risk of colorectal adenoma, interactions of a detoxification gene variation with different environmental exposures in gauging lung cancer risk, and different polymorphisms and parental characteristics associated with varying risks of molecularly defined subgroups of childhood leukemia.

Because only a small proportion of gliomas are likely to be caused by the effects of inherited rare mutations or high-dose radiation, researchers have focused on polymorphisms in genes that might influence susceptibility to brain tumors in concert with environmental exposures.

Polymorphisms in Carcinogen Metabolism and Gliomas

Glutathione S-transferases and CYPs, as part of the Phase 1 and 2 detoxification process, are involved in the metabolism of many electrophilic compounds, including carcinogens, mutagens, cytotoxic drugs, and metabolites, as well as in the detoxification of products of reactive oxidation. Several case–control studies of the statuses of GSTs and CYPs 1A1, 2D6, and 1E1 have yielded few positive and replicable associations.

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Although the results of some studies indicated specific findings for tumor subtypes (for example, the GSTM1 deletion was more common in GBM cases with the TP53 mutation than in those without (OR 2.8, 95% CI 0.93–8.4), the GSTM1 deletion was less common (p = 0.03) and GSTP1 A114V V-carriers were more common than expected (p = 0.06) among oligodendroglioma cases. The significant multiplicative effects of GSTP1 1105V and CYP2E1 Rsal variants suggest that gene interactions may be important.

Gliomas and DNA Repair Gene Polymorphisms

The study of the inherited variation in DNA repair involves another category of genes that have been extensively investigated with respect to cancer because of the importance of DNA repair in maintaining genomic integrity. In 2002, Goode and colleagues reviewed 30 studies reporting on DNA repair polymorphisms in adult gliomas and cancer of the bladder, breast, lung, skin, prostate, head and neck, stomach, and esophagus; the number of studies published has more than quadrupled in the past 3 years. Gliomas and glioma subtypes have been significantly associated with variants in ERCC1, ERCC2, the nearby gene GLTSCR1 (glioma tumor suppressor candidate of unknown function), PRKDC (also known as XRCC7), and MGMT, but the too few studies have been performed to assess consistency. The complexity of the DNA repair pathway is increasingly being revealed, with 130 known genes involved in base excision repair, direct reversal of damage, mismatch repair, nucleotide excision repair, homologous recombination, non-homologous end joining, sanitization of nucleotide pools, activity of DNA polymerases, editing and processing of nucleases, and postreplicative repair; genes associated with sensitivity to DNA damaging agents; and others suspected of influencing DNA repair functioning are also involved. Studies focusing on constellations of DNA repair variants involved in these pathways might help elucidate their roles in gliomagenesis and progression.

Gliomas and Polymorphisms in Cell Cycle Regulation

Dysregulation of the cell cycle (control of proliferation and apoptosis) is a hallmark of most gliomas reviewed by Ichimura, et al. and MDM2 is a key molecule in maintaining the fidelity of this process. In one study, the G variant of SNP309 in the MDM2 promoter led to higher expression of MDM2, with concomitant reduced expression of TP53, and was found to be significantly associated with an earlier patient age at tumor development and multiple tumor sites in patients with Li–Fraumeni syndrome, in whom brain tumors are one component.

Infections and Immunological Risk Factors for Gliomas

Among the most intriguing and consistent findings of the past decade are statistically significant inverse associations between gliomas that develop during adulthood and histories of allergies, chicken pox, and anti–varicella-zostervirus immunoglobulins G and E. Among the handful of genetic syndromes (caused by inherited rare mutations) associated with increased risk of brain tumors (for a review see other studies), account for a small proportion of cases, they provide an important starting point for identifying candidate genes and pathways that could be involved in gliomagenesis. Syndromes that include gliomas or medulloblastomas (with gene names and chromosome location) are neurofibromatosis Types 1 and 2 (NF1, 17q11; NF2, 22q12), tuber-
ous sclerosis (TSC1, 9q34; TSC2, 16p13), retinoblastoma (RB1, 13q14), Li–Fraumeni syndrome (TP53, 17p13), and Turcot syndrome and multiple hamartoma (APC, 5q21; hMLH1, 3p21.3; hMSH2, 2p22-21; PMS2, 7p22; and PTEN, 10q23.3). The roles of more common variants in many of these genes (and related pathways) in sporadic gliomas are unknown.\(^\text{74}\)

Demonstration of familial aggregation does not prove a genetic origin, but it is often among the first indicators that genetic susceptibility may play a part in the pathogenesis of a complex disease. Relative risks of brain tumors among family members of patients who harbor them have ranged from 1 to 10; in large, well-conducted studies, familial glioma risks are approximately twofold, similar in magnitude to the familial association involved in breast cancer and other cancers for which susceptibility genes have been identified (for a review see Bondy, et al.,\(^\text{14}\) and other studies\(^\text{65,101,182}\)). The pattern of brain tumor occurrence in families has been attributed to environmental causes in one study\(^\text{67}\) and to multifactorial causes, polygenic causes, and autosomal recessive inheritance in others.\(^\text{14,40,102}\) Paunu, et al.\(^\text{119}\) recently published evidence of a statistically significant linkage to 15q23-q26.3 in 15 Finnish families with multiple cases of glioma (after stringent control for multiple testing. \(p = 0.03\)).

Gamma radiation–induced mutagen sensitivity is more commonly found in peripheral lymphocytes in glioma cases than in control cases,\(^\text{15,16}\) and it has been suggested that such a mutagen sensitivity is at least partly attributable to inherited variation in capacity to repair radiation damage.

**FUTURE STUDIES IN THE MOLECULAR EPIDEMIOLOGY OF GLIOMAS**

Suspected and novel inherited variations in glioma susceptibility and prognosis are likely to be confirmed and identified through multidisciplinary studies involving pathologists, geneticists, epidemiologists, functional genomics, bioinformaticians, biostatisticians, immunobiologists, and clinicians. These studies will require integration of the following: 1) traditional and molecular pathological analysis involving cyto genetic and epigenetic classifications of tumors to reduce and refine glioma subgroups; 2) new genomic technologies and bioinformatic/biostatistical tools with which to interrogate and explore candidate genes, regions, and pathways and to enhance new discoveries; 3) high-quality population resources for causal studies to aid in the selection of cases and controls with well-documented familial and demographic data as well as environmental exposure and personal medical history; and 4) case groups with clearly defined treatment histories for prognostic studies. We hypothesize that demographic, environmental, and immunological factors are likely to influence the susceptibility of patients and disease prognosis, and that different constellations of factors may be involved with different histological and molecular subtypes of glioma.

This brief summary of published case–control studies of polymorphisms involving glioma status and prognosis illustrates several important and widespread problems in current research into the association between genes and diseases, including the paucity of studies assessing consistency for many reported associations, the reporting of false-positive results, and the lack of consideration of functional significance of the polymorphisms studied.\(^\text{7,24,129,165,172}\)

Although the most likely explanation of discrepant results among studies is the chance reporting of positive findings in small studies, it is also possible that discrepancies derive from different effects in different populations arising from different exposure and developmental experiences and/or disease heterogeneity. Lack of information on the functional relevance of polymorphisms can also limit reasonable inferences. Future studies will need to include replication or use other means to reduce reporting of false positives.

Different study designs are encouraged because no ideal design is available for the discovery of genetic and environmental associations regarding heterogeneous and relatively rare diseases such as gliomas. Both familial linkage studies and case–control studies may prove helpful in discovering genes associated with glioma susceptibility. For adequate sample sizes and expertise, consortia will be essential for familial linkage studies, studies of gene–environment interactions with even a relatively common glioma subtype such as GBM, and basic epidemiological studies of less common subtypes such as oligodendroglial tumors and other low-grade glial tumors. The Brain Tumor Epidemiology Consortium (an international group of brain tumor researchers) already has several initiatives in process in these and other areas of brain tumor research.\(^\text{79}\)

**SUMMARY**

The reasons for variations in glioma incidence according to time of diagnosis, sex, age, ancestry/ethnicity, and geography are poorly understood, as are factors affecting prognosis. There are few established risk factors for gliomas; ionizing radiation and rare mutations in highly penetrant genes associated with certain diseases and syndromes can only be cited to explain relatively few cases. Both familial aggregation of gliomas and the inverse association of allergies and immune-related conditions with gliomas have been shown consistently, but the explanations for these associations are inadequately developed or unknown. Ongoing research on gliomas focuses on classifying homogeneous groups of tumors on the basis of molecular markers and identifying genetic polymorphisms that, in conjunction with developmental experiences and environmental exposures, may increase brain tumor risk. Rather than examine individual genetic polymorphisms in isolation, new research focuses on genetic polymorphisms in pathways involved in carcinogenesis. Related pathways are also studied simultaneously so that confounding by genes with similar functions can be avoided. Large sample sizes are required for such studies, and these large studies will avoid false-positive findings and permit examination of the modifying effects of polymorphisms on environmental exposures, as well as of the potential for interaction between germline mutations and sporadic tumor mutations. Khoury and colleagues\(^\text{85}\) recently argued for the importance of genomic studies of diseases with known strong environmental contributors by stating,

because almost all human diseases result from interactions between genetic variants and the environment, suggesting that genomic research will not contribute to preventing conditions with known environmental risk factors could perpetuate the false competition between nature and nurture.

For diseases such as gliomas, for which most cases have
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yet to be linked to either an environmental or a genetic cause, the greatest potential for discovery may lie in genomic studies in conjunction with continued evaluation of environmental and developmental factors.

Some limited success has been achieved in advancing the treatment of gliomas (as in the case of oligodendrogliomas), but improving the survival rates for patients harboring astrocytic tumors will probably require many randomized clinical trials of novel treatment strategies. In conclusion, most gliomas have extremely poor prognoses and we have limited knowledge of their causes, how to treat them, and other factors that determine prognoses. Thus, there is a great need for large, well-designed epidemiological studies of potential genetic and environmental risk factors and for randomized controlled trials of prognostic factors and treatment strategies for gliomas.

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