Molecular Epidemiology of Primary Brain Tumors

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Summary: Although primary brain tumors (PBTs) are generally considered to be a multifactorial disorder, understanding the genetic basis and etiology of the disease is essential for PBT risk assessment. Understanding of the genetic susceptibility for PBT has come from studies of rare genetic syndromes, linkage analysis, family aggregation, early-onset pediatric cases, and mutagen sensitivity. There are currently no effective markers to assess biological dose of exposures and genetic heterogeneity. The priorities recently recommended by the Brain Tumor Epidemiology Consortium emphasized the need for expanding research in genetics and molecular epidemiology. In this article, we review the literature to identify molecular epidemiologic case-control studies of PBTs that were hypothesis-driven and focused on four hypothesized candidate pathways: DNA repair, cell cycle, metabolism, and inflammation. We summarize the results in terms of genetic associations of single nucleotide polymorphisms of these pathways. We also discuss future research directions based on available evidence and technologies, and conclude that high resolution whole genome approach with significantly large sample size could rapidly advance our understanding of the genetic etiology of PBTs. Literature searches were done on PubMed in March 2009 with the terms glioma, glioblastoma, brain tumor, association, and polymorphism, and we only reviewed English language publications. **Key Words:** Molecular epidemiology, brain tumors, genome-wide association, polymorphisms.

INTRODUCTION

The United States is among those countries where higher incidence rates of primary brain tumors (PBTs) are found.[1,2] It is estimated that there are 22,000 new cases of PBTs and 13,000 deaths annually in the U.S. The Central Brain Tumor Registry of the United States (CBTRUS)[3] annual reports indicated that brain tumor incidence was increasing over a 10-year period from 1985 to 1994. CBTRUS data also showed that glioma accounts for 77% of PBTs, and patients with glioma have very poor survival. Although high-dose ionizing radiation and rare genetic syndromes are the only well established risk factors,[4,5] they seem to account for only a small portion of all PBT cases. This observation supports hypotheses that PBTs genetically are a multifactorial disease rather than a condition that follows a mode of Mendelian inheritance or results from a single exposure. Moreover, variations at multiple loci might determine the expression of each gene. Hundreds of susceptible loci that are involved in single disorders are not always located in genes associated with disease risk. The variations at multiple loci contribute to the expression of each gene involved.[6]

Recently, genome-wide association studies (GWAS) with very large sample sizes and carefully matched controls have provided a powerful tool to identify genes involved in common human genetic diseases.[7-11] This emergent technology can detect effects at the single nucleotide level. The identification of susceptibility alleles provides a greater understanding of carcinogenesis, potentially offering targets for therapeutic interventions. Unlike lifestyle exposure, single nucleotide polymorphisms (SNPs) do not change during the process of carcinogenesis. Therefore, SNPs could be suitable biomarkers in risk assessment. SNPs identified through this approach are associated with modest risk of PBTs, but this is just the beginning of the investigation of the complicated genetic basis of phenotypic variation. The most pressing challenge is how to link GWAS results with observed clinical and phenotypic changes. Possibly with genetic technology we might also be able to determine the racial differences of PBT incidence—in partic-

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ular why African Americans have such low incidence of developing PBTs.

This article reviews the literature for findings concerning the exploration of the genetic etiology of PBTs (mainly glioma) and identification of the knowledge gap in PBT research. Future direction is discussed based on available evidence and technologies.

GENETIC CHANGES ASSOCIATED WITH SUSCEPTIBILITY

PBT is considered to be a multifactorial disease. Accumulative DNA damage responsible for tumor transformation is the result of interactions between environmental exposure and genetic susceptibility. Although it is still hard to quantitatively determine the magnitude of environmental exposure and genetic susceptibility, the accuracy of risk assessment is improved with the improvement of genotyping resolution and whole genome approaches. Genetic susceptibility of PBT comes from rare genetic syndromes, family history of multiple cancers, chromosome changes, and linkage analysis. The improved resolution of genetic testing helps us understand the role of genetic polymorphisms, specifically in pathways such as DNA repair, cell cycle, inflammation, angiogenesis, and metabolic genes in the process of brain tumor carcinogenesis. It has been suggested that the initial genetic event of PBT involves genetic polymorphism and mutation of DNA repair and apoptosis genes. Subsequent somatic mutations in cell cycle control and angiogenesis genes are essential for malignant transformation. Rare genetic disorders such as Li-Fraumeni syndrome, neurofibromatosis (NF) type 1 and type 2, tuberous sclerosis, Turcot's syndrome, and familial polyposis support inherited predisposition to PBTs.[12-14] Comparative genomic hybridization (CGH) analysis of familial PBTs aimed to reveal disease-specific chromosomal changes and thus identified a spectrum of chromosomal losses and gains.[15,16] The epidemiologic evidence is suggestive for association between PBT and family history of cancer. Many studies have reported familial aggregation of glioma.[17-23] As familial aggregation of cancers could be a sign of genetic etiology, we suspect that there are alleles responsible for familial aggregation observed in PBT patients and that these alleles could be revealed by GWAS analysis. The same assumption might be true for early-onset pediatric PBT cases.

Cytogenetic markers used for molecular epidemiology in PBTs

Molecular cytogenetic analysis of familial PBTs primarily focused on studying genes possibly associated with the disease, especially *TP53*, *PTEN*, *CDKN2A*, and *CDK4* genes. However, germline mutations did not increase significantly for familial PBTs.[24,25] In 2002, Paunu et al[26] performed the first linkage study for familial glioma, investigating 15 familial glioma pedigrees by using a two-stage disease gene mapping strategy for low-penetrance alleles. Their result indicated that *15q23-q26.3* harbors a novel susceptibility allele for familial glioma, and since their finding, improved higher resolution molecular genetic technology has marked the progress of mapping genetic changes in PBTs. Bredel et al[27] conducted a high-resolution mapping by using cDNA microarray CGH technology to profile genetic changes with 42,000 cDNA clones in a cohort of 54 glioma patients and identified five novel minimally deleted loci thought to be important in gliomagenesis. The study successfully predicted astrocytoma and oligodendroglioma with 92% and 88% accuracy, respectively, based on 170 gene copy number patterns. Their findings implied that some early genetic changes necessary for gliomagenesis may be shared within the same histological groups and might be used for tumor classification. The first genome-wide analysis of pediatric PBTs for DNA copy number changes and loss of heterozygosity (LOH) by using SNP array was reported by Wong et al,[28] who used a chip containing 11,562 SNPs, and analyzed 14 high-grade and 14 low-grade pediatric glioma. Wong et al found no detectable LOH for low-grade glioma, various degrees of LOH for high-grade cases, and amplification on *EGFR* and *PDGFRA* loci. They eventually validated their results by sequencing and quantitative PCR.

PBTs molecular epidemiologic studies with focus on DNA repair

DNA repair genes are a key factor in maintaining genomic stability. We have listed about 20 epidemiological studies reporting positive associations between DNA repair polymorphisms and cancer risk (Table 1[29-45]). Only a small proportion of studies were large (five studies were more than 500 pair cases and controls) and population based; however, some consistencies in results are apparent. Primarily, of the 17 genes associated with glioma risk, eight were from the double-strand breaks repair (DSBR) pathway, suggesting a strong link between DSBR and glioma. Although the etiology of gliomas remains unclear, ionizing radiation (IR) has been identified as the well established risk factor. IR induces various types of DNA damages, particularly DSBs that are the major threats to the genomic integrity of cells. Considering that DSBR is the most important DNA repair pathway to deal with such damage, it is very likely that the SNPs in the DSBR could play an important role in carcinogenesis. Second, three genes, *ERCC1*, *ERCC2*, and especially *MGMT*, a gene involved in repairing alkylated quinine in DNA, were consistently associated with glioma risk across three different studies from three different populations (whites, Japanese, and Caucasians),

Table 1. *PBT Molecular Epidemiologic Studies with Focus on DNA Repair*

Disease Type	Pathway Gene	Association Y/N	Population	Sample Size	References (Year)
Glioma	Double strand break repair				
	XRCC3	Y	Chinese	771 cases, 752 controls	29 (2009)
		Y	Caucasian	844 cases, 1560 controls	30 (2008)
	XRCC4, LIG4	Y	Chinese	771 cases, 752 controls	31 (2008)
	XRCC5, XRCC6	Y	Chinese	771 cases, 752 controls	32 (2007)
	XRCC7	Y	Caucasian	309 cases, 342 controls	33 (2004)
	BRCA1, EME1	Y	Caucasian	112 cases, 112 controls	34 (2008)
	Base excision repair				
	APEX1, XRCC1, PARP1 (ADPRT)	Y	Caucasian	373 cases, 365 controls	35 (2009)
	XRCC1	Y	Caucasian	844 cases, 1560 controls	30 (2008)
	Nucleotide excision repair				
	ERCC1	Y	White	122 cases, 159 controls	36 (2000)
		Y	White	450 cases, 500 controls	37 (2005)
		Y	Caucasian	373 cases, 365 controls	35 (2009)
	ERCC2 (XPD)	Y	White	187 cases, 169 controls	38 (2001)
		Y	White	141 cases, 108 controls	39 (2005)
		Y	White	450 cases, 500 controls	37 (2005)
	LIG1	Y	Caucasian	373 cases, 365 controls	35 (2009)
	Direct reversal of damage				
	MGMT	Y	White	453 cases, 526 controls	40 (2007)
		Y	Japanese	74 cases, 255 controls	41 (2003)
		Y	Caucasian	373 cases, 365 controls	35 (2009)
	Chromatin Structure				
	CHAF1A	Y	Caucasian	1013 cases, 1016 controls	42 (2008)
	Others				
	EXO1	Y	Caucasian	112 cases, 112 controls	34 (2008)
	WRN	N	Brazilian	94 cases, 100 controls	43 (2008)
Meningioma	*ERCC2, Ki-ras*	Y	Israel	440 cases	44 (2005)
	RAD54L	Y	Spain and Ecuador	70 cases, 287controls	45 (2003)

which strongly suggests that they may be involved in carcinogenesis. A recent European study revealed that *CHAF1A*, a gene coded for Chromatin assembly factor, is associated with increased glioma risk. Additional epidemiological analyses of these and other DNA repair gene polymorphisms will provide essential information about the *in vivo* relationships between the DNA repair mechanisms and carcinogenesis and will complement *in vitro* analysis.

PBTs molecular epidemiologic studies with focus on cell cycle

Glial cell proliferation is considered important in gliomagenesis. Studies that looked at the correlations between cell cycle genes and glioma risk did not generate a clear pattern (Table 2[43,46-70]). The positive association between *EGF/EGFR* and glioma risk was observed in majority of the case-control studies published. However, studies of *PTEN* and *TP53* genes and glioma risk gave contradictory results. *CASP8*, a gene that plays a critical role in the execution phase of programmed cell death, *CDKN2A* (cyclin-dependent kinase inhibitor 2A), an important tumor suppressor gene that is frequently deleted in many tumors, and *CX3CR1*, a chemokine receptor 1 gene, have recently been reported to be risk-bind genes and will need further validation. *HRAS* and *MDM2*, genes involved in signal transduction pathway and inactivation of tumor protein p53, were reported to be not associated with glioma risk. *MMP7*, *NF1*, and *TP53* were linked to the risk of astrocytoma, but the results require further confirmation. *CASP8* is also reported to be associated with the risk of meningioma. Results for astrocytoma and meningioma risk were not sufficient to draw any conclusions.

PBTs molecular epidemiologic studies with focus on metabolism

Our review indicated that currently available studies do not provide enough supportive information to establish genes involved in metabolism for PBT risk assessment (Table 3[71-83]). Contradictory results were observed for *MTHFR*, *MTRR*, *NAT2*, and *PON1* for glioma. *SOD2*, *SOD3*, and *CAT* were positively linked to glioma risk in a recent study. The association was not indicated for *CYP1A1*, *GSTT11*, *GSTM1*, *GSTM3*, and *NQO1*. This is inconsistent with data from meta-analysis. A meta-analysis of eight studies with 1,630 gliomas, 245 meningiomas, and 7,151 controls found no association between glutathione S-transferases (GST) variants and adult brain tumors.[84] Neural carcinogens, such as dietary N-nitroso

Table 2. *PBT Molecular Epidemiologic Studies with Focus on Cell Cycle*

Disease Type	Pathway Gene	Association Y/N	Population	Study Info	References (Year)
Glioma	*TP53*	Y		135 cases	46 (2005)
		Y	USA	22 cases only (mutations)	47 (1995)
		Y	Chinese	44 cases only (mutations)	48 (1999)
		N	Brazilian	94 cases, 100 controls	43 (2008)
		N	Japanese	113 cases	49 (2004)
	EGF	Y	USA	42 cases only (mutations)	50 (2004)
		Y	Caucasian	188 cases, 176 controls	51 (2006)
		Y		197 case, 570 controls	52 (2007)
		N	Caucasian	209 cases, 214 controls	53 (2007)
	EGFR	Y		70 cases only (mutations)	54 (1997)
		N	Brazilian	193 cases, 200 controls	55 (2008)
		Y	USA	174 cases; cohort	56 (2001)
		N	Japanese	113 cases	49 (2004)
	PTEN	Y	Japanese	26 cases only (mutations)	57 (2004)
		N	Turkish	62 cases only	58 (2007)
		Y	USA	174 cases; cohort	56 (2001)
	MDM2	N		98 cases, 102 controls	59 (2008)
		N	Japanese	254 cases, 50 controls	60 (2007)
	CDKN2A	Y		45 cases only	61 (2003)
		N		36 families, with 44 patients	62 (1997)
	NF1	Y		12 cases only	63 (2003)
	PIK3CA	Y	US	73 cases only	64 (2006)
	MMP1	Y		81 cases, 57 controls	65 (2005)
	MMP7	Y	Chinese	221 cases, 366 controls	66 (2006)
	HRAS	N	White	73 cases, 65 controls	67 (2000)
	CASP8	Y	Caucasian	1005 cases, 1011 controls	68 (2008)
	CDKN2B, CDK4	N		36 families, with 44 patients	62 (1997)
	CX3CR1	Y	France	208 cases only	69 (2008)
Meningioma	*CASP8*	Y	White, Black, and Other	623 cases, 799 controls	70 (2007)

compounds (NOCs) from consumption of cured meats, were studied for the risk of gliomas. A pooled analysis of nine population-based studies failed to establish NOCs as a causal agent for glioma.[85]

PBTs molecular epidemiologic studies with focus on inflammation

An inverse association between *IL-4RA*, *IL-13,* and glioblastoma was observed and the relationship was not affected by allergic conditions (Table 4[86-92]). The studies also provide evidence to establish allergies as a risk factor for glioma and thus urge the identification of more candidate genes to be studied under this category. Furthermore, a meta-analysis of 3,450 gliomas and 1,070 meningiomas from eight observation studies found a strong inverse relationship between history of asthma, eczema, hay fever, or allergy and brain tumor.[93] SNP analysis of *IL-4*, *IL-4RA*, and *IL-13* was demonstrated to be a better approach for overcoming the recall bias of self-reporting allergies and increased post diagnostic immunoglobulin E levels. However, it remains unclear whether allergies protect against tumors or whether immunosuppressive gliomas inhibit allergies. The consistency of these findings suggests a possible role in gliomagenesis for immunologic factors and inflammation, clearly warranting more investigation of immune function genes.

DISCUSSION AND FUTURE DIRECTIONS

In summary, among the polymorphisms in DNA repair, cell cycle, metabolism, and inflammation pathways, the DNA repair and inflammation pathways, in particular the DSBR sub-pathway, may play important roles in the initiation of glioma. However, despite the promise of all of the molecular epidemiology information accumulated over the years, there is currently little or no knowledge of the functional relevance of these polymorphisms that are being studied. Therefore, in addition to emphasizing large, well designed epidemiological studies, gene environment and gene-gene interactions, future studies should emphasize the functional relevance of polymorphisms and their correlation with repair phenotypes to help further illuminate the complex landscape of molecular epidemiology and PBT risk. (Studies in which the pathway gene was not specified are shown in Table 5.[39,94-101])

Table 3. *PBT Molecular Epidemiologic Studies with Focus on Metabolism*

Disease Type	Pathway Gene	Association Y/N	Population	Study Info	References (Year)
Acoustic neuroma, Glioma, Meningioma	*CYP1A1, CYP1B1, GSTM3, NQO1, EPHX1*	N	White, Black and Other	782 cases, 799 controls	71 (2006)
	CYP2E1	Y	White, Black and Other	673 cases, 799 controls	72 (2003)
	SOD2, SOD3, CAT	Y	Non-Hispanic White	465 cases, 494 controls	73 (2008)
Glioma	*GSTM1*	Y		394 cases only	74 (2002)
		N	Caucasian	725 cases, 1612 controls	75 (2007)
	NAT2	Y	Caucasian, African-American	90 cases, 90 controls	76 (1998)
		N		159 cases, 163 controls	77 (2001)
	PON1	Y	Turkish	84 cases, 50 controls	78 (2006)
		N	White, African-American, Asian and Other	66 cases, 236 controls	79 (2005)
	MTHFR, MTR	Y	UK Caucasian	1005 cases, 1101 controls	80 (2008)
		N	Caucasian	328 cases, 400 controls	81 (2006)
	NQO1	N	Caucasian	725 cases, 1612 controls	75 (2007)
		N		159 cases, 163 controls	77 (2001)
	GSTP1	Y		394 cases only	74 (2002)
	GSTs	N	Caucasian, African-American, and Other	367 cases, 428 controls	82 (2004)
	GSTM3, GSTT1, CYP1A1	N	Caucasian	725 cases, 1612 controls	75 (2007)
	MDR1	N	Caucasian	458 cases, 528 controls	83 (2005)

We constructed a working hypothesis diagram for gliomagenesis because most of the studies reviewed were predominantly dealing with glioma (FIG. 1). Understanding the genetic etiology of PBT is essential to understand the familial aggregation, ethnic differences, age preferences, and high-risk exposure of the disease. High-penetrance genetic abnormalities that influence PBTs involve the *NF1* gene, *p53* gene, *MMR* genes, *APC* gene, and only rarely the *PTEN*, p16 (INK4A)/p14 (ARF), and *CDK4*. However, risk from high-penetrance germline mutations only accounts for a very small portion of overall risk when compared to those from low-penetrance germline mutations. It is evidenced that many newly identified susceptibility SNPs via high-throughput whole genome approaches are significantly associated with only low risk of the disease, suggesting multiple gene groups involved in different steps of the genetic pathway. Although it is not established that the effects at the single nucleotide level might be causative for the disease, we presented studies of the genetic polymorphisms of both high and low penetrance genes, especially multiple genes that regulate various DNA repair path-

Table 4. *PBT Molecular Epidemiologic Studies with Focus on Inflammation*

Diseases Type	Pathway Gene	Association Y/N	Population	Study Info	References (Year)
Glioma	*IL4R*	Y	Caucasian	694 cases only	86 (2008)
		Y	Caucasian	456 cases, 541 controls	87 (2007)
		Y		111 cases, 422 controls	88 (2005)
		Y	Caucasian	217 cases, 1171 controls	89 (2007)
	IL4	Y		756 cases, 1190 controls	90 (2007)
		Y	Caucasian	456 cases, 541 controls	87 (2007)
	IL13	Y		111 cases, 422 controls	88 (2005)
		Y	Caucasian	373 cases, 365 controls	91 In press (2009)
		Y	Caucasian	456 cases, 541 controls	87 (2007)
	IL10, COX2	Y	Caucasian	373 cases, 365 controls	91 In press (2009)
	IL6	Y		756 cases, 1190 controls	90 (2007)
	PTGS2, ADAM33	Y		111 cases, 422 controls	88 (2005)
	TNFb4	Y	Italy	58 cases, 95 controls	92 (1999)

Table 5. *PBT Molecular Epidemiologic Studies with Pathway Gene not Specified*

Diseases Type	Pathway Gene	Association Y/N	Population	Study Info	References (Year)
Glioma	*IDH1*	Y		22 cases only (mutations)	94 (2008)
		Y		445 cases, 494 controls	95 (2009)
	IDH2	Y		445 cases, 494 controls	95 (2009)
	hTERT	Y	France	352 cases, 305 controls	96 (2007)
	CTNNB1, APC	N	UK	77 cases only	97 (2006)
	GLTSCR1	Y	Caucasians	141 cases, 108 controls	39 (2005)
	IGF1, IGF1R, IGF2, IGF2R, IGFBP3	N	Non-Hispanic White	487 cases, 495 controls	98 (2008)
Meningioma	*ALAD*	Y	Caucasian, African-American, and Other	686 cases, 799 controls	99 (2006)
		Y	Caucasian, African-American, and Other	782 cases, 799 controls	100 (2005)
Glioma and Memingioma	*SULT1A1*	Y	Turkish	60 cases, 156 controls	101 (2008)

ways, which is important to understand the predisposition to PBTs. Initial predisposing events involve genes regulating DNA repair and apoptosis that lead to further somatic events and the formation of PBTs. It occurs more frequently in families with a history of multiple cancers, early-onset pediatric PBTs, and occasionally in random PBTs. On the other hand, the majority of PBT risk is from unknown somatic mutations and the interaction between all mutations and environmental exposure. Few studies have detailed measurements of exposures or gene-exposure interactions. Better exposure measurements, such as internal dose and biological effective dose, need to be developed so that both genetic susceptibility and exposure may be accurately estimated for overall PBT risk assessment. The heterogeneity of exposures, susceptibility, and tumor types requires current and future research to identify additional germline polymorphisms. A long-term goal would be to incorporate these associations with epidemiologic data to develop a risk-assessment model, an effort which could

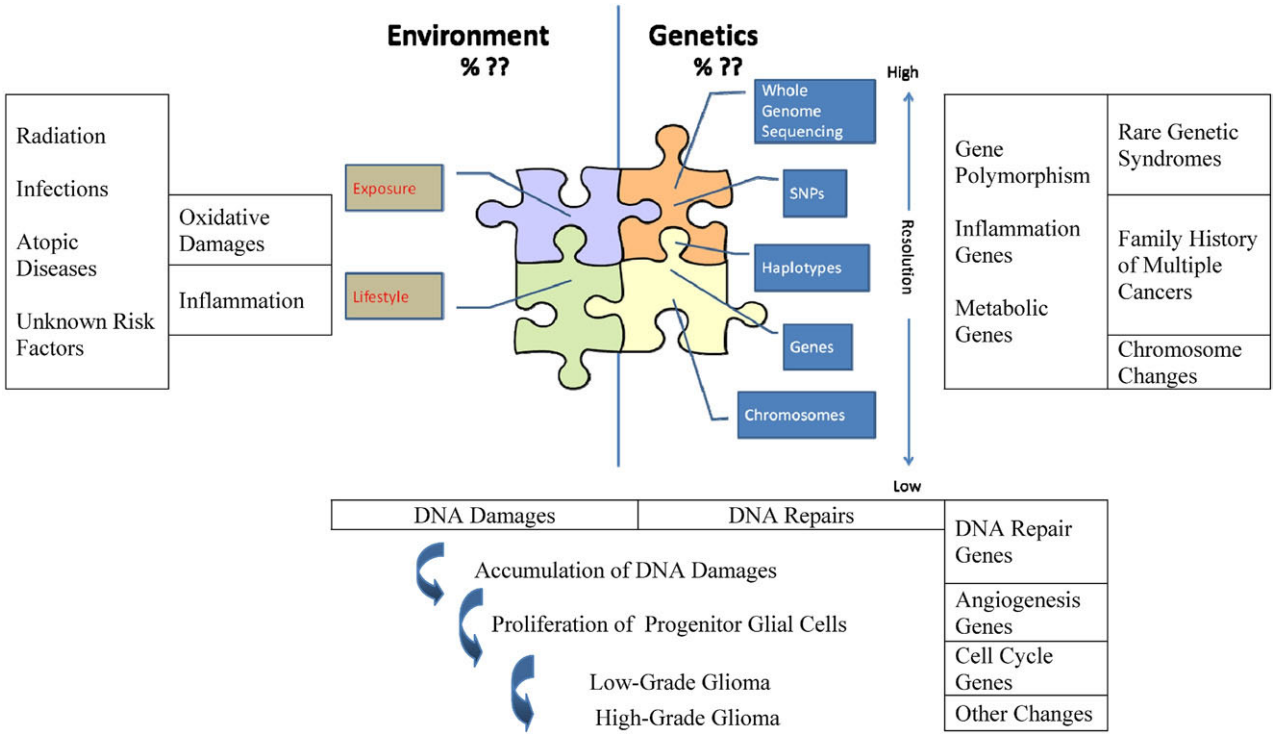

FIG. 1. Working hypothesis of gliomagenesis.

also improve classification of PBTs into more homogenous groups by using molecular markers.

In order to study familial aggregation by using the whole genome SNPs approach, an international consortium, GLIOGENE,[102] was assembled in 2007 with the aim of identifying families with two or more glioma cases for linkage analysis. GLIOGENE is considered the first international collaborative effort to investigate familial glioma regarding shared genetic defects. Recent molecular epidemiologic studies of PBTs included larger samples sizes and better designed SNP analysis, but most of these studies were based on the molecular pathway proposed and covered limited genetic loci. As the technology improves, a whole genome non-hypothesis driven approach with higher resolution will be able to identify disease-specific susceptibility loci in order to better understand the genetic etiology associated with PBT risk. To further expedite our understanding of the molecular basis of cancer, a comprehensive and coordinated effort from the Cancer Genome Atlas (TCGA), funded by the National Institutes of Health, has been put forward to apply several profiling modalities in a high throughput fashion to three cancer types. Glioblastoma,[103] squamous cell lung cancer, and ovarian carcinoma were selected due to their poor prognosis and the relatively large amounts of high-quality tissue samples in biorepositories. The modalities used to characterize the numerous samples include DNA sequencing of a select number of genes, gene expression by microarray, CGH arrays, methylation arrays, and microRNA microarrays. The output from TCGA and other high-throughput projects is still being evaluated, and it is likely that further exciting findings will be made in these datasets.

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