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Genomic Abnormalities in Gliomas

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1. Introduction

In general, studies reveal that cancer arises through genetic and epigenetic alterations that affect specific genes within a given cell type. These changes involve a gain of function when the alterations involve oncogenes, a loss of function when the target genes are tumor suppressor genes. Thus, both genetic and epigenetic changes promote the instability of cellular homeostasis (Bello & Rey, 2006; Richardson, 2003; Sugimura & Ushijima, 2000). This lack of stability reflects the complexity of cancer because the loss of controlled cell growth occurs due to changes in one or more genes. These genetic and epigenetic events are followed by the growing accumulation of changes in hundreds, if not thousands, of genes. Over time, this accumulation causes the tumor to reach its highest degree of malignancy, which usually culminates in metastasis (Bartek & Lukas, 2001). However, in recent years, a subpopulation of tumor cells has been found to display a slow rate of cell division, high tumorigenic potential and characteristics similar to those of normal stem cells. This discovery has changed the concept of metastasis to one associated with strictly terminal states (Stiles & Rowitch, 2008).

Hanahan & Weinberg (2000) proposed that all tumor cells must acquire six essential alterations in cell physiology that collectively dictate malignant growth: (1) loss of normal signaling for cell proliferation arrest, (2) loss of signaling for cell differentiation, (3) autocrine signaling for cell division, (4) reduction in apoptosis, (5) ability to enter the basement membrane and other tissues and organs, and (6) induction of angiogenesis. All of these processes involve biochemical pathways that form a complex network of cell signaling. These processes are usually altered in tumors because the genes that compose them are changed, resulting in cell cycle dysregulation. Therefore, the identification and determination of oncogenes and tumor suppressor genes is essential for understanding both cancer biology and clinical applications, such as the identification of therapeutic targets, early detection, and prediction of the disease course. Studies concerning cell cycle control genes have served as a starting point for identifying genes related to tumorigenesis and their biochemical role in various pathways (Paige, 2003).

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Changes in oncogenes can lead to constitutive activation, which involves activation under conditions in which an oncogene would normally be inactive. For this process to occur, a cell needs only one allele of an oncogene to be altered, resulting in a selective growth advantage. In contrast, changes in tumor suppressor genes often reduce the gene product and consequently its activity. For this reason, cells that develop a selective advantage with changes in tumor suppressor genes usually require inactivation of both alleles of the target gene. Conceptually, tumor suppressor genes can be subdivided into two categories: "gatekeepers" that directly inhibit tumor growth and thereby suppress tumor formation and "caretakers" that ensure DNA integrity by repairing damage or preventing genomic instability (Vogelstein & Kinzler, 2004).

Studies of hereditary and sporadic forms of tumors, particularly retinoblastoma, culminated in the formulation of Knudson's "two events" model in 1971. In hereditary tumors, the first mutation occurs in one allele in the germline and results in a predisposition to develop tumors. Throughout development, a second change (mutation or loss of heterozygosity) inactivates the other allele and silences the altered gene. In contrast, sporadic tumors acquire the two allelic alterations that lead to gene silencing throughout the organism's development (Knudson, 1971). Over time, the neoplastic transformation and metabolic-phenotype of the cell can evolve. Ultimately, these changes result in a cancer in which clonal expansion of modified somatic cells destroys the adjacent normal tissue (Bartek & Lukas, 2001).

For many years, research in cancer genetics has prioritized understanding the role of genetic alterations in carcinogenesis. Studies revealed that base deletions, insertions, recombination and amplification in oncogenes and tumor suppressor genes were related to metastasis and invasion. These changes were also closely related to tumorigenesis and tumor progression. For this reason, the scientific community accepted that genetic changes almost exclusively explained the process of carcinogenesis (Sugimura & Ushijima, 2000). However, studies also indicated that embryogenesis and differentiation, which are characterized by specific patterns of gene expression in tissues and organs, can occur without changes in the DNA sequence. This notion has interested the scientific community in potential epigenetic mechanisms of carcinogenesis (Jones & Buckley, 1990; Rush & Plass, 2002).

An epigenetic phenomenon is defined as a change in gene function that is heritable through mitosis or meiosis but cannot be explained by changes in the DNA sequence. Aberrant epigenetic mechanisms, such as promoter hypermethylation, histone modifications, or non-coding RNA expression, are known to be important for tumor formation and comprise the "third pathway" in Knudson's model. These mechanisms result in transcriptional repression equivalent to that observed with the mutations and deletions proposed in Knudson's model (Jones & Baylin, 2007).

DNA methylation, the main epigenetic modification studied, occurs at cytosine residues in the cytosine-guanine sequences (CpG) of DNA through the action of an enzyme family called DNA methyltransferases (DNMT). In humans, approximately 70% of CpG sites, which are generally located in repetitive DNA sequences, are methylated. Clusters of unmethylated CpG sites are present in the genome as well, and these clusters are referred to as CpG islands. Approximately 60% of genes have CpG islands in the promoter regions and in the first exon. CpG islands are often dimethylated when associated with housekeeping genes. Moreover, CpG islands are tissue specific and are generally methylated except in those tissues where the associated gene is expressed (Cross & Bird, 1995; Gonzalez-Gomez et al., 2003). A recent genome-wide analysis revealed that CpG islands are also found in

non-promoter regions. In addition, epigenetic abnormalities causing loss of gene function are more frequent than genetic abnormalities in cancer cells (Schuebel et al., 2007). Thus, cellular epigenetic inheritance mediated by aberrant DNA methylation resulting in gene silencing, gene imprinting, and⁄or activation of cancer-associated genes is now accepted as an important factor defining the transformed phenotype (Natsume et al., 2010)

2. Tumors of the central nervous system

Tumors of the central nervous system (CNS) are relatively rare and represent approximately 5-9% of all cancers, with an estimated incidence of 4.2 to 5.4 per 100,000 people/year. Moreover, tumors of the CNS carry a very poor prognosis and are associated with considerable morbidity and mortality. They are a leading cause of childhood cancer deaths, the second leading cause of cancer-related death in men aged 20–39, and the fifth leading cause of cancer-related death in women aged 20–39 (Ohgaki & Kleihues, 2005).

Although the incidence of CNS tumors is small compared with the incidence of other cancers, CNS tumors are among the most serious human malignancies because they affect the organ responsible for the coordination and integration of all biological activities. Moreover, as each region of the brain has a vital function, therapies used to treat other cancers (e.g., total surgical removal of an organ or tumor with a generous margin of normal tissue) cannot be applied to brain tumors. The inability to use these therapies hinders quality of life and patient survival (Louis et al., 2002).

In CNS tumors, the histopathological classifications are extensive and based primarily on descriptive morphology. Because the histogenesis of these tumors is unique and heterogeneous, it is difficult to characterize several of the tumor subtypes, which is reflected in the difficulties encountered in tumor diagnosis (Gilbertson, 2002).

In contrast with the first World Health Organization (WHO) classifications for CNS tumors (Kleihues et al., 1993; Zülch, 1979), the third edition by Kleihues & Cavenee (2000) incorporated genetic profiles as additional aids in defining brain tumors. The fourth edition of the WHO classifications for CNS tumors, which was published in 2007, lists several new characteristics. The fourth edition is based on consensus from an international working group of 25 pathologists and geneticists, as well as contributions from more than 70 international experts. Currently, this edition is the standard for defining brain tumors for clinical oncology and cancer research communities world-wide (Louis et al., 2007).

3. Gliomas

Gliomas are the most common tumors of the CNS. However, in spite of marked progress in characterizing the molecular pathogenesis of gliomas, these tumors remain incurable. In most cases, gliomas are also refractory to treatment because of their molecular heterogeneity. Gliomas rarely metastasize outside of the brain but instead infiltrate extensively into the surrounding normal brain. Therefore, surgery is not curative but can establish the diagnosis and relieve symptoms by decompressing the brain, which is located in the rigid intracranial cavity. Radiation therapy and chemotherapy increase survival; however, disease recurrence is frequently inevitable (Park & Rich, 2009).

The following four degrees of malignancy are recognized by the WHO: grades I and II (low-grade), which are biologically less aggressive and grades III and IV (high-grade), which are the most aggressive. The histological criteria for grading malignancies are not uniform for

all subtypes of gliomas. Thus, all tumors should be classified before the degree of malignancy is determined. This classification is made according to the cell type thought to be responsible for the tumor and based on the characteristics exhibited by astrocytes, oligodendrocytes, ependymal cells, or their neuronal progenitors (Louis et al., 2007). Table 1 shows the heterogeneous WHO classification for gliomas according to the degree of malignancy.

	WHO Grade					WHO Grade			
Astrocytic tumors	**I**	**II**	**III**	**IV**	**Ependymal tumors**	**I**	**II**	**III**	**IV**
Subependymal giant cell astrocytoma	•				Subependymoma	•			
Pilocytic astrocytoma	•				Myxopapillary ependymoma	•			
Pilomyxoid astrocytoma		•			Ependymoma		•		
Diffuse astrocytoma		•			Anaplastic ependymoma			•	
Pleomorphic xanthoastrocytoma		•							
Anaplastic astrocytoma			•		**Choroid plexus tumors**				
Glioblastoma				•	Choroid plexus papilloma	•			
Giant cell glioblastoma				•	Atypical choroid plexus papilloma		•		
Gliosarcoma				•	Choroid plexus carcinoma			•	
Oligodendroglial tumors					**Other neuroepithelial tumors**				
Oligodendroglioma		•			Angiocentric glioma	•			
Anaplastic oligodendroglioma			•		Chordoid glioma of the third ventricle		•		
Oligoastrocytic tumors									
Oligoastrocytoma		•							
Anaplastic oligoastrocytoma			•						

Table 1. WHO grading of gliomas (Louis et al., 2007).

Gliomas of astrocytic, oligodendroglial, and ependymal origin account for 80% of CNS tumors. For this reason, some morphological and genetic characteristics of these tumors are discussed below.

3.1 Astrocytomas

Astrocytomas represent the vast majority of gliomas and account for 70% of the total gliomas seen in patients. Astrocytomas can be further characterized as pilocytic astrocytomas (WHO grade I) or diffuse astrocytomas, including low-grade astrocytomas (WHO grade II), anaplastic astrocytomas (WHO grade III) and glioblastomas (WHO grade IV) (Kleihues et al., 2002).

Pilocytic astrocytomas are more commonly seen in children and carry a good prognosis because of their biology. Patients with neurofibromatosis type 1, a familial syndrome caused by germline mutations in the gene *NF1* (neurofibromin 1), have an increased incidence of pilocytic astrocytomas. These tumors are usually not aggressive and stand out among astrocytomas because they have maintained their WHO grade I status for years and even decades, in contrast to diffuse astrocytic tumors (WHO grades II-IV). However, some cases can progress to a higher degree of malignancy, though such a progression is rare (Listernick et al., 1999).

More than 100 cases of pilocytic astrocytomas were analyzed by cytogenetics and many others were used for comparative genomic hybridization (CGH); however, the vast majority of the results indicated normal patterns (Bigner et al., 1997; Sanoudou et al., 2000; Zattara-Cannoni et al., 1998). In adults, genetic changes were more frequent but were still rare. The few molecular genetics studies on these tumors indicated allelic loss of both gene loci *TP53* (tumor protein p53) and *NF1* in regions 17p and 17q, respectively. In sporadic tumors, few mutations were reported in the *TP53* locus and none in *NF1* (Gutmann et al., 2000; Kluwe et al., 2001).

The relevance of a malignancy-grading scheme based on histopathology is indicated by the correlation with patient survival. Patients with low-grade astrocytomas (WHO grade II) have a median survival of approximately seven years, whereas patients with anaplastic astrocytomas (WHO grade III) have a mean survival of half that time (McCormack et al., 1992). Patients with glioblastomas have a median survival time of 9 to 11 months (Simpson et al., 1993).

Unlike pilocytic astrocytomas, diffuse astrocytic tumors are often seen in adults. Low-grade astrocytomas have a peak incidence between 25 and 50 years of age, whereas glioblastomas have a peak incidence between 45 and 50 years (Colins, 2004).

Ng & Lam (1998) suggested dividing glioblastomas into two distinct molecular and clinical entities: primary or de novo glioblastomas, which occur in elderly patients and are clinically very aggressive and secondary glioblastomas, which develop from low-grade astrocytomas and have a more prolonged clinical course.

Many mechanisms are involved in the initiation and progression of secondary glioblastomas, including the loss of *NF1* and *TP53* genes and the activation of signal transduction pathways, such as *PDGF* (platelet-derived growth factor) and its receptor *PDGFR* (PDGF receptor). These pathways are involved in the induction of low-grade tumors (e.g., pilocytic astrocytomas), which can progress to high-grade tumors (e.g., anaplastic astrocytomas and secondary glioblastoma). This progression is associated with the lack of a functional *RB1* (retinoblastoma 1) because of the loss of *RB1* or gene amplification/overexpression of *CDK4* (cyclin-dependent kinase 4) (Fig. 1a). In primary

glioblastomas, the same genetic pathways are disrupted but by different mechanisms. For example, reduction of the *TP53* pathway generally occurs through the loss of the gene *ARF4* (ADP-ribosylation factor 4) or less frequently through amplification of the gene *MDM2* (transformed 3T3 cell double minute 2). The lack of *RB1* also occurs via a loss of the gene *CDKN2A* (cyclin-dependent kinase inhibitor 2A). In primary glioblastomas, amplification and/or mutation of *EGFR* (epidermal growth factor receptor) and loss of *PTEN* (phosphatase and tensin homolog) are the most frequently observed genetic defects (Fig. 1b) (Zu & Parada, 2002).

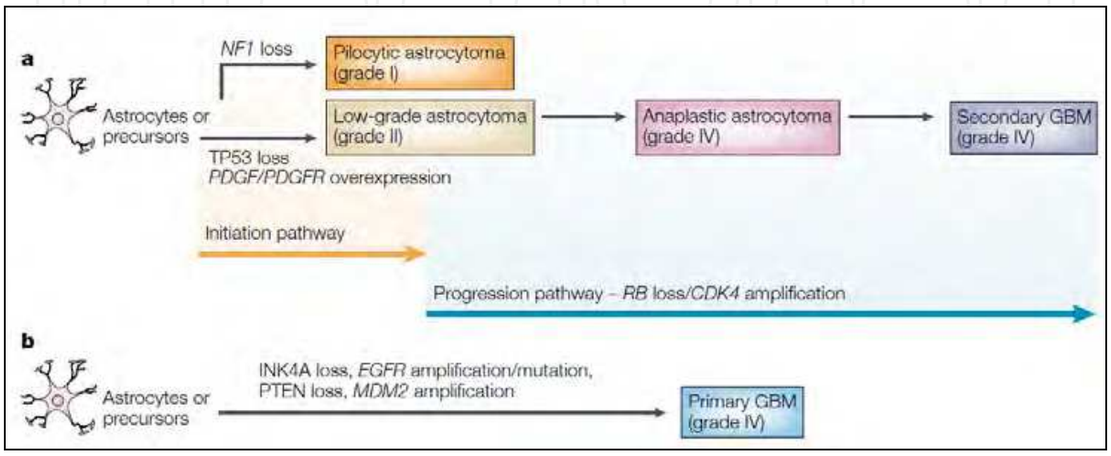


Fig. 1. Genetic pathways involved in the development of (a) primary and (b) secondary glioblastomas (Zhu & Parada, 2000).

Sequencing of the genome recently identified mutations in the *IDH1/IDH2* genes (isocitrate dehydrogenase 1 and 2 genes) that occur in the majority of WHO grade II–III gliomas and secondary glioblastomas (Hartmann et al., 2009; Yan et al., 2009), all of which harbor a better prognosis compared with the wild-type cases (Sanson et al., 2009). However, pilocytic astrocytomas (WHO grade I) that are potentially curable by complete resection rarely harbor *IDH* mutations. *IDH* appears to function as a tumor suppressor when inactivated through mutation, rendering the IDH enzyme unable to catalyze conversion of isocitrate to alphaketoglutarate. This process also induces HIF1-alpha (hypoxia-inducible factor), which triggers the angiogenic process. However, the precise mechanism of its effect on tumor biology remains unclear (Dang et al., 2009).

Aberrant activation of the *BRAF* proto-oncogene (v-raf murine sarcoma viral oncogene homolog B1) at 7q34, which is most commonly caused by gene duplication and fusion or less frequently by point mutation, has only recently been identified as the characteristic genetic aberration in pilocytic astrocytomas. *BRAF* abnormalities occur in 60–80% of pilocytic astrocytomas but almost never in diffuse, infiltrating astrocytomas (Jones et al., 2009). Thus, testing for *BRAF* gene alterations might be helpful for differentiating during diagnosis between pilocytic astrocytomas and low-grade, diffuse astrocytomas (Korshunov et al., 2009).

The importance of silencing DNA repair pathways, especially the DNA-repair enzyme AGAT (O6-alkylguanine DNA alkyltransferase), which is encoded by the gene *MGMT* (O6-methylguanine-DNA-methyltransferase), has been the subject of substantial debate in recent years (Hofer & Lassman, 2010). The *MGMT* gene is frequently silenced by promoter

hypermethylation in diffuse gliomas, and this hypermethylation has been pinpointed as an epigenetic mechanism that reduces *MGMT* expression levels. There are 97 CpG islands in the *MGMT* promoter, and these CpG islands are further divided into two hypermethylated regions (Nakagawachi et al., 2003). Because of its critical role in DNA repair, the epigenetic silencing of *MGMT* is associated with an increased number of mutations and with a poorer outcome in glioblastomas. Thus, *MGMT* silencing is considered to be a biomarker for poor prognosis (Komine et al., 2003). However, an association between *MGMT* promoter methylation and the response of malignant gliomas to alkylating chemotherapy using nitrosourea compounds, temozolomide, or a combination of both has been observed (Esteller et al., 2000; Herrlinger et al., 2006). Furthermore, Hegi et al. (2005) reported that patients treated with radiotherapy and temozolomide, and whose tumors had a methylated *MGMT* promoter (which is seen in approximately 40% of primary glioblastomas), survived significantly longer than did patients whose tumors lacked *MGMT* promoter methylation. Rivera et al. (2010) recently reported that *MGMT* promoter methylation in anaplastic gliomas (WHO grade III) is also predictive of the response to radiotherapy and linked to longer survival in the absence of adjuvant chemotherapy. The use of temozolomide based on *MGMT* methylation status highlights the importance of understanding epigenetic changes in glioblastomas for the discovery of novel therapies and prognostic factors for the treatment of this deadly cancer (Komine et al., 2003; Nakagawachi et al., 2003)

3.2 Oligodendrogliomas

Oligodendrogliomas represent approximately 10-15% of gliomas, are more common in adults, and can be divided into two histological subtypes: low-grade (WHO grade II) and anaplastic (WHO grade III) (Kleihues et al., 2002).

Low-grade oligodendrogliomas are less biologically aggressive than are astrocytic tumors. Therefore, the prognosis is quite favorable and survival beyond 15 years is achieved in up to 90% of cases that receive a complete surgical resection. There is potential for malignancy, but even the aggressive tumors respond well to additional treatments (e.g., radiation and chemotherapy). Anaplastic oligodendrogliomas have a more aggressive course; however, survival is still five to eight years longer than that observed with anaplastic astrocytomas (Reifenberger & Louis, 2003).

In 1990, the PCV chemotherapy regimen (procarbazine, carmustine, and vincristine) was shown to result in a dramatic tumor response in oligodendrogliomas. Since that time, the identification of all forms of gliomas with oligodendroglial components became crucial (Macdonald et al., 1990). Importantly, these studies indicated that the prognostic power of oligodendroglial components was independent of whether radiotherapy, chemotherapy or combined radio-chemotherapy was used (Wick et al., 2009). This phenomenon is likely due to oligodendrogliomas exhibiting specific genetic abnormalities that distinguish them from other gliomas. Reifenberger et al. (1994), after a thorough analysis of the genome, reported a loss of genetic information in the 1p and 19q loci in oligodendrogliomas, the so-called chromosome 1p/19q co-deletion. This loss was later linked with a good response to PCV and provided the first molecular indicator of treatment response in brain tumors (Cairncross et al., 1998; Reifenberger et al., 2003). Further studies corroborated these findings, and it is now known that the chromosomal loss results from an unbalanced translocation (Franco-Hernandez et al., 2009; Jenkins et al., 2006). Approximately 85% of low-grade oligodendrogliomas and 65% of anaplastic oligodendrogliomas present with 1p/19q co-deletions (Smith et al., 2000).

Low-grade oligodendrogliomas and astrocytomas present a loss of *ARF4* expression and overexpression of *EGFR* and PDGF signaling. Malignant progression is associated with additional genetic abnormalities that are similar to those described above for astrocytomas, including a lack of the *RB1* pathway, loss of *RB1,* or gene amplification/overexpression of the *CDK4* gene (Franco-Hernandez et al., 2007; Reifenberger & Louis, 2003).

3.3 Ependymomas

Ependymomas arise in or near the ependymal surface, and these tumors can occur anywhere in the ventricular system, spinal cord and even occasionally at extraneural sites. The most common location is in the fourth ventricle, followed by the spinal cord, the lateral ventricles and the third ventricle. These tumors are more common in children but can also occur in adults (Ebert et al., 1999).

WHO classification identifies four major subtypes of ependymomas: subependymomas (WHO grade I), myxopapillary ependymomas (WHO grade I), low-grade ependymomas (WHO grade II) and anaplastic ependymomas (WHO grade III). Subependymomas are intraventricular in location, while myxopapillary ependymomas are commonly found in the cauda equina. The low-grade ependymomas can be differentiated from their anaplastic counterparts based on the low rate of mitosis and the low level of nuclear polymorphism; however, the distinction between the two tumors remains poorly defined (Kleihues et al., 2002).

In ependymomas, chromosomal abnormalities detected by classic cytogenetics and CGH involve chromosomes 1, 6, 7, 9, 10, 13, 17, 19 and 22. Deletions are the most commonly observed changes, and chromosome 22 losses are common in adults (50%) but rare in pediatric ependymomas (Kraus et al., 2001; Lamszus et al., 2001; von Haken et al., 1996). The target genes, located in regions of chromosomal gain or loss, are unknown, with the exception of cases in which both copies of the wild-type *NF2* gene (neurofibromin 2) are lost in intramedullary ependymomas (Alonso et al., 2002). Isolated cases of *MEN1* gene (multiple endocrine neoplasia I) loss have also been reported (Urioste et al., 2002). Germline mutations in *TP53* are uncommon, in contrast with those seen in diffuse astrocytomas (Nozaki et al., 1998).

When reviewed together, the data on genetic and epigenetic abnormalities presented above allow us to define four molecular biomarkers: *MGMT* hypermethylation in glioblastomas and anaplastic gliomas, *IDH1* and *IDH2* mutations in diffuse gliomas, *BRAF* aberrations in pilocytic astrocytomas, and combined deletions of chromosome arms 1p and 19q in oligodendroglial tumors. These biomarkers and their clinical significance are summarized in Table 2.

4. Single nucleotide polymorphisms and gliomas

A single nucleotide polymorphism (SNP) is generally defined as a stable replacement of only one DNA base, with a frequency greater than 1% in at least one population (Taylor et al., 2001). In human genetics studies, SNPs are simply referred to as bi-allelic markers because tri-and tetra-allelic markers are rare (Brookes, 1999).

Initially, only a few thousand SNPs were thought to exist in the entire genome. However, since 2000, that number has increased about one thousand-fold. In 2001, an international consortium on mapping SNPs described 1.42 million polymorphic loci. More important than this large number is the precision of their placement in the genome; there is approximately

one polymorphism every 1.91 Kb. Therefore, 90% of sequences greater than 20 Kb in length have at least one SNP, and this density can be higher in genic regions. Of the known genes, 93% contain SNPs and 98% are at least 5 Kb away from a SNP. Soon, almost all genes or gene regions will be marked by one of these variable sequences (Sachidanandam et al., 2001).

Molecular marker	Clinical significance
IDH1/*IDH2* mutation	• Diagnostic marker for diffuse WHO grade II and III gliomas, as well as secondary glioblastomas, and associated with a better prognosis in these tumors • Rare in primary glioblastomas, but when present, it is associated with a more favorable outcome • Not predictive for response to a particular type of therapy
BRAF duplication/fusion	• Diagnostic marker for pilocytic astrocytomas and helpful in distinguishing these tumors from diffuse astrocytomas • Prognostic significance within the group of pilocytic astrocytoma patients is unknown
MGMT promoter methylation	• Predictive for response of glioblastomas to alkylating chemotherapy • Associated with longer survival in glioblastoma patients treated with radiotherapy combined with concurrent and adjuvant temozolomide • Prognostic in anaplastic glioma patients treated with radiotherapy and/or alkylating chemotherapy
1p/19q co-deletion	• Associated with improved prognosis in oligodendroglial tumor patients receiving adjuvant radiotherapy and/or chemotherapy • Not predictive for response to a particular type of therapy

Table 2. The four most relevant markers for the molecular diagnosis of gliomas (Hofer & Lassman, 2010; Riemenschneider et al., 2010).

Because they are found throughout the genome, some alleles containing SNPs produce functional or physiologically relevant gene products. For example, SNPs in a coding region can affect the coded protein. When located in an intron, SNPs can influence the splicing mechanism, and when located in the promoter, SNPs can alter gene transcription (Krawczak et al., 1992). For this reason, SNPs are recognized as important tools in human genetics and medicine and have been widely used in genetic association studies of various complex diseases, including cancer. In humans, several reviews of SNPs have been carried out in an attempt to determine the patterns of SNP haplotypes in different populations (Conrad et al., 2006; Gonzalez-Neira et al., 2006; Jakobsson et al., 2008; Nothnagel & Rohde, 2005; Salisbury et al., 2003). Data from these tests are extremely useful for studying the genetic basis of cancer. For this reason, several research groups have focused on elucidating the role of SNPs in different genes related to the initiation and progression of gliomas in different populations. We performed association studies between SNPs, the risk of developing gliomas, and the prognosis for gliomas in a Brazilian population. Brazilians form one of the most heterogeneous populations in the world, which is the result of five centuries of

interethnic crosses of peoples from three continents: the European colonizers who are mainly represented by the Portuguese, the African slaves, and the autochthonous Amerindians (Parra et al., 2003).

Until recently, we were the only laboratory investigating the association between *WRN* Cys1367Arg, the risk for brain tumor development, and the prognosis of brain tumors, especially with regard to gliomas (Pinto et al., 2008a). Werner syndrome (WS) is a premature aging disorder characterized by early onset of symptoms related to normal aging and is caused by inherited, recessive mutations in the *WRN* gene. The *WRN* gene encodes a member of the RecQ family of helicases involved in DNA replication and in maintaining the integrity of the genome (Harrigan et al., 2006). The cells of WS patients exhibit a high level of chromosomal translocations and deletions, and these patients present an increased predisposition to various types of cancer, including CNS tumors (Kobayashi et al., 1980). However, despite its putative tumor suppressor function, little is known about the contribution of the WRN protein to sporadic human malignancies. Taking into account that almost all cancers occur in the elderly and that mutations in the *WRN* gene lead to accelerated aging, it has been suggested that polymorphisms of the *WRN* gene, similar to Cys1367Arg, might be associated with age-related pathologies and cancer predisposition. However, our data indicate that neither glioma risk (OR = 1.38; 95% CI, 0.78-2.43; $P = 0.334$) nor patient survival (overall and disease-free survival, $P = 0.396$ and $P = 0.843$, respectively) was associated with variant alleles.

Similar results were found when we evaluated the genotype distribution of *TP53* Pro47Ser and Arg72Pro SNPs for their involvement in susceptibility to gliomas and in determining the oncologic prognosis of patients (Pinto et al., 2008b). A critical site in the TP53 protein for apoptosis signaling is a proline-rich region located between codons 64 and 92. Dumont et al. (2003) reported that the homozygous Arg72 allele induces apoptosis at a rate that is 15-fold higher than the Pro72 allele. According to Leu et al. (2004), the apoptosis-inducing ability of the Arg72 allele is in part due to its mitochondrial location, which makes it possible for TP53 to directly interact with the pro-apoptotic protein, BAK. However, the *TP53* Pro47Ser SNP resulted in a significantly decreased ability of the TP53 protein to induce apoptosis. A critical event in TP53-induced apoptosis is phosphorylation of the serine residue at codon 46. This region is where allele Pro47 acts as a substrate for proline-directed kinases such as the MAPK1 protein. Li et al. (2005) reported that the Ser47 allele, which is a poor substrate for MAPK1, has an apoptosis-inducing ability that is 5-fold lower than that of the wild-type Pro47 allele. However, our data again indicated that neither glioma susceptibility nor patient survival was associated with the *TP53* Arg72Pro or Pro47Ser alleles in the Brazilian population.

In 2009, we investigated the role of *EGF* +61 A>G as a potential risk factor and/or prognostic marker for gliomas in the Brazilian population. The *EGF* gene encodes a ligand for EGFR that activates a cascade of events responsible for promoting cell proliferation, inhibition of apoptosis, and differentiation. Alterations in the EGF/EGFR signaling pathway are associated with tumor progression in a variety of human cancers. Therefore, high expression of EGF may play a key role in glioma development and progression (Salomon et al., 1995). Shahbazi et al. (2002) first reported that the +61 A>G SNP in the 5'-UTR region of *EGF* is associated with increased EGF production and risk of malignant melanoma. Since that discovery, other research groups have obtained conflicting findings regarding the relationship of this functional SNP with different human cancers, including gliomas (Bao et al., 2010; Bhowmick et al., 2004; Costa et al., 2007; Liu et al., 2009; Vauleon et al., 2007; Wang

et al., 2010). In our results, the genotype and allele frequencies between cases and controls were similar, indicating no significant association with glioma risk (P = 0.94 and P = 0.887, respectively) and suggesting that *EGF* +61 A>G may not significantly contribute to the susceptibility to gliomas in the Brazilian population. This result is consistent with that of Vauleon et al. (2007) and Liu et al. (2009) in French and Chinese populations, respectively. However, we found that the major +61G allele (frequency among controls, 0.51) was associated with a shorter overall survival in patients (P = 0.023). Thus, with regard to patient survival, our results corroborate those of Bhowmick et al. (2004) in a population of North American patients.

We have also studied the *GSTP1* gene, which encodes a protein accounting for approximately 90% of the enzymatic activity of the glutathione S-transferase (GST) family (Custodio et al., 2010). GSTs constitute a superfamily of ubiquitous, multifunctional enzymes that are involved in cellular detoxification of a large number of endogenous and exogenous chemical agents that possess electrophilic functional groups (Ryberg et al., 1997). The GSTP1 protein is a pi-class enzyme and *GSTP1* structure has been extensively examined in association with the risk of cancer (White et al., 2008). The influence of the *GSTP1* Ile105Val SNP on cancer has been reported with inconsistent results from different parts of the world (Syamala et al., 2008). Our results demonstrate that the Val105 allele was more frequent in a population of cancer patients than in a healthy population (0.29 and 0.06, respectively; $P < 0.001$) and that the presence of this genotype may increase the risk of developing astrocytomas and glioblastomas (OR = 8.60; 95% CI, 4.14-17.87; $P < 0.001$). However, we did not find an association between the *GSTP1* Ile105Val SNP and patient survival.

Recently, we began studying SNPs in DNA repair genes and we performed association analysis of SNPs in genes for the *XRCC* (X-ray cross-complementing) family, *XRCC1* and *XRCC3*, in a series of gliomas (unpublished data). Human tumors may develop through alterations to the DNA repair system, which is crucially important for cellular life (Kawabata et al., 2005). To ensure the integrity of the genome, a complex system of DNA repair was developed. Base excision repair is the first defense mechanism of cells against DNA damage and a major means for preventing mutagenesis (Hu et al., 2005). Repair genes may play an important role in maintaining genomic stability through different pathways mediating base excision repair (Sreeja et al., 2008). For this reason, much attention has been given to the study of SNPs in *XRCCs* and their involvement in different types of cancer, including gliomas. We performed analysis of the Arg194Trp and Arg399Gln SNPs in *XRCC1* and the Thr241Met SNP in *XRCC3* to assess their roles in the risk and prognosis for gliomas in Brazilians. Our results provide evidence that the *XRCC*1 Arg194Trp SNP may contribute to the etiology of human gliomas because the Trp194 allele was strongly associated with risk and the Gln399 allele revealed a small, increased risk for tumor development. In regard to the *XRCC3* Thr241Met SNP, we also found evidence that *XRRC3* Thr241Met may contribute to the etiology of human gliomas. However, when the Arg194Trp and Arg399Gln SNPs in *XRCC1* and the Thr241Met SNP in *XRCC3* were considered together, we did not find statistical difference between genotypes and patient survival.

Around the globe, other groups have analyzed the association between SNPs found in *XRCCs* genes and the risk of developing gliomas. Kiuru et al. (2003) evaluated the association between the *XRCC1* Arg194Trp, Arg280His, and Arg399Gln SNPS, the *XRCC3*

Thr241Met SNP, and glioma risk in a prospective, population-based, case-control study conducted in Denmark, Finland, Sweden, and the UK. They found no significant association with gliomas for any of the SNPs when examined individually. However, the results indicated possible associations between combinations of *XRCC1* and *XRCC3* SNPs and the risk of glioma development, as carriers of both homozygous variant genotypes, i.e., *XRCC1* Gln399Gln and *XRCC3* Met241Met were associated with a three-fold increased risk of glioma (OR = 3.18; 95% CI, 1.26-8.04). In a haplotype-based approach in a Chinese population, Liu et al. (2007) investigated the role of 22 tagging SNPs (tSNPs) of *XRCC5*, *XRCC6* and *XRCC7*. They found that glioma risk was significantly associated with three of the *XRCC5* tSNPs (rs828704, rs3770502 and rs9288516, P = 0.005, 0.042 and 0.003, respectively), one *XRCC6* tSNP (rs6519265, P = 0.044), and none of the *XPCC7* tSNPs in a single-locus analysis. Haplotype-based association analysis revealed that glioma risk was significantly associated with one protective *XRCC5* haplotype "CAGTT," which accounted for a 40% reduction (OR = 0.60, 95% CI, 0.43-0.85) in glioma risk. In a study of North Americans, Wang et al. (2004) found that the variant XRCC7T allele of the *XRCC7* G6721T SNP was significantly more common in the glioma cases than in the controls (P = 0.045). The *XRCC7* genotype frequency was also significant when comparing the cases and controls (P = 0.040). Likewise, the difference in distribution of the combined T-variant genotype (GT + TT) between the cases and controls was also statistically significant (P = 0.012), suggesting that the T allele may be a risk factor for glioma.

In addition to the studies mentioned above, several others were published indicating the results of associations, positive or negative, of genomic variations with the risk of developing gliomas. However, the ethnic variations, methodological variations, and the presence of responsible, functionally unknown SNPs in linkage disequilibrium with those SNPs analyzed have contributed to the dissemination of conflicting results in different parts of the world. Gu et al. (2009) presented a review including a list of eight literature-defined, putative, functional, SNPs associated with gliomas in at least two populations from case-control studies. A summary of this list is presented in Table 3.

Gene selection for association studies has previously been based on studies reporting the role of genes and their SNPs in the regulation of cellular functions. However, after the completion of the human genome project and the development of analytical platforms capable of parallel genotype processing, which resulted in new selection strategies for identifying susceptibility genes in many complex genetic disorders, gene selection is currently based on genome-wide association (GWA) studies.

The two glioma GWA studies performed so far were published in 2010 in the same issue of Nature Genetics. In the first pages, Shete et al. (2009) presented the results of a meta-analysis of two GWA studies that involved the genotyping of 454,576 tSNPs in a total of 1,878 glioma cases and 3,670 controls, with posterior validation in three additional independent series totaling 2,545 cases and 2,953 controls. The authors identified five risk loci for glioma at 5p15.33 (*TERT* rs2736100), 8q24.21 (*CCDC26* rs4295627), 9p21.3 (*CDKN2A-CDKN2B* rs4977756), 11q23.3 (*PHLDB1* rs498872), and 20q13.33 (*RTEL1* rs6010620). In the second study, Wrensch et al. (2009) analyzed 275,895 SNPs in 692 adult patients with high-grade glioma and 3,992 controls, with a replication series of 176 high-grade glioma cases and 174 controls. That analysis provided further evidence to implicate 9p21 (*CDKN2B* rs1412829) and 20q13.3 (*RTEL1* rs6010620) in glioma risk.

Main paths, genes	Associated SNPs	Effect	OR (95% CI)
DNA repair			
XRCC7	G6721T	Risk	GG vs. TT, 1.82 (1.13–2.93)[1]
			GG vs. TT, 1.44 (1.13–1.84)[2]
XRCC1	Arg399Gln	Risk	AA vs. GG, 1.23 (0.96–1.57)[2]
			AA vs. GG, 1.32 (0.97–1.81)[3]
			GA/AA vs. GG, 1.44 (1.05–1.92)[4]
PARP1	Val762ala	Protective	CT/CC vs. TT, 0.80 (0.67–0.95)[2]
			CT/CC vs. TT, 0.71 (0.52–0.97)[4]
ERCC1	A8092C	Risk	AA/AC vs. CC, 4.41 (1.6–12.2)[5]
			AA/AC vs. CC, 1.67 (0.93–3.02)[6]
ERCC2	Gln751Lys	Risk	CC vs. AA, 1.19 (0.93–1.52)[2]
			AA vs. AC/CC, 1.66 (1.01–2.72)[6]
MGMT	Phe84Leu	Protective or risk?	CT/TT vs. CC, 0.66 (0.45–0.94)[4]
			CT/TT vs. CC, 1.26 (0.90–1.75)[7]
Cell cycle, *EGF*	+61 A>G	Risk	$P = 0.032$[8]
			AG/GG vs. AA, 1.52 (1.03–2.23)[9]
Inflammation: *IL13*	Arg130Gln	Protective	AG vs. GG, 0.75 (0.48–1.17)[10]
			TT vs. CC/CT, 0.39 (0.16–0.93)[11]

Table 3. Selected glioma susceptibility genes and SNPs observed in at least two studies. [1]Wang et al. (2004); [2]McKean-Cowdin et al. (2009); [3]Kiuru et al. (2008); [4]Liu et al. (2009); [5]Chen et al. (2000); [6]Wrensch et al. (2005); [7]Felini et al. (2007); [8]Bhowmick et al. (2004); [9]Costa et al. (2007); [10]Schwartzbaum et al. (2005); [11]Amirian et al. (2010).

5. Cancer stem cells

Both the invasive nature of the tumor and its heterogeneity probably contribute to the poor response to the treatment regimens available today. Tumor heterogeneity is traditionally attributed to the accumulation of regional variations in the tumor microenvironment and the diversity of subpopulations of cancer cells, which result from random genetic changes (Reya et al., 2001).

The majority tumors consist of a heterogeneous population of cells with different proliferative potential, as well as the ability to re-form the tumor upon transplantation into immunodeficient mice (Visvader & Lindeman, 2008). Recently, evidence has accumulated that tumors contain a population with characteristics similar to normal stem cells called

cancer stem cells, which are also multipotent cells. This subpopulation has the ability to repair itself and is believed to control tumor initiation, a process that is responsible for tumor recurrence and the resistance to therapy observed in different tumor types, including gliomas (Bao et al., 2006). The observation that normal stem cells and cancer stem cells share common features (e.g., undifferentiated state and unlimited capacity for self-regeneration) led to the hypothesis of cancer stem cells (Park & Rich, 2009).

A practical component of the cancer stem cell hypothesis is directed to the matter of intrinsic resistance to radiation and chemotherapy. Cancer stem cells are predicted to be difficult targets for tumor therapy because they exhibit a slowed cell cycle and high levels of drug export. Furthermore, these cells may not express or may not be dependent on the oncoproteins that are targeted by the most recent generation of cancer drugs (Cheng et al., 2010).

Cancer stem cells, similar to normal stem cells, are dependent on the microenvironment in which they are located. This microenvironment, formed by cells and extracellular matrix, controls the maintenance of organ functions. Therefore, disturbance of the local microenvironment in neoplastic processes can trigger tumor development (Barcellos-Hoff et al., 2009). In glioma, for example, studies have shown that the microenvironment is surrounded by blood vessels, which provide access to signaling molecules, nutrition, and possibly to the use of the nascent vasculature for migration, which provides direct cell contact and secreted factors that are responsible for maintaining the state of quiescence of cancer stem cells, regulating their self-renewal and multipotency (Gilbertson & Rich, 2007; Jandial et al., 2008). Thus, one can say that cancer stem cells and the microenvironment are parts of the tumor. Therefore, knowledge of the associated characteristics will lead to a new understanding of tumor biology and the development of new therapeutic strategies against these cells. For this reason, it is extremely important to characterize the different subpopulations of cancer stem cells that contribute to tumor formation (Denysenko et al., 2010).

6. Conclusion

The development and progression of gliomas may likely be due to a multistep process that involves the functional inactivation of tumor suppressor genes and DNA repair genes, as well as the activation of oncogenes. Given the limitations of current therapies, understanding the pathways that lead to tumor progression should remain a high priority in cancer research. If the mechanisms that culminate in metastasis are fully understood, the development of new diagnostic and therapeutic methods may allow for a substantial improvement in the quality of life of affected patients and a better means of predicting patient prognosis. Genetic and epigenetic studies involving large cohorts of glioma patients in different populations have provided important information for understanding the role of key genes in the development and risk of gliomas. Because it is considered a work in progress, the WHO classification for brain tumors may soon incorporate molecular data to refine the classification of these diseases, which are complex from a therapeutic standpoint.

SNPs have become increasingly popular in the genetic study of gliomas because of the quick, inexpensive and accurate analysis of SNPs. The identification of SNPs as risk factors for different glioma subtypes can be important for prevention, diagnosis and prognosis. Variations in the genomic sequence contribute to phenotypic diversity and susceptibility to or protection against many complex diseases. Thus, it is estimated that the risk of gliomas

may be strongly influenced by the patterns of SNPs in certain key susceptibility genes; these SNPs are still being identified. The same reasoning can be applied to inter-individual variations in genetic responses to medications, which is a field of great interest to the pharmaceutical industry. The benefit of having a SNP map of different populations is that it allows for coverage of the entire genome so that researchers can compare the patterns and frequencies of SNPs in their patients and associate these patterns with the disease concerned. The GWA studies with significant numbers and carefully matched controls have become a powerful tool in identifying genes involved in common genetic diseases, including gliomas. The identification of susceptibility alleles provides a greater understanding of gliomagenesis and provides target genes for potential therapeutic intervention. Unlike environmental exposure, SNPs do not change during the process of tumorigenesis. Therefore, SNPs may be useful as indicators of risk.

The main features of normal stem cells are the capacity for self-regeneration and differentiation to different cell types. These characteristics are heavily regulated by the local microenvironment. Because studies have shown that cancer stem cells behave like normal stem cells, understanding the regulatory mechanisms of cancer stem cells and their microenvironment has changed our understanding of the biology of gliomas and has precipitated a reassessment of current therapies. The cure of glioma will require the elimination of all tumor cells, including cancer stem cells. Therefore, further studies to provide a better understanding of the origin of cancer stem cells and their interactions with the microenvironment are needed. These findings hold great promise for the development of new therapies that can help us improve the results achieved with current therapies and thereby prolong patient survival.

7. References

Alonso, M.E., Bello, M.J., Arjona, D., Gonzalez-Gomez, P., Lomas, J., de Campos, J.M., Kusak, M.E., Isla, A. & Rey, J.A. (2002). Analysis of the NF2 gene in oligodendrogliomas and ependymomas. *Cancer Genet Cytogenet*, Vol.134, No.1, pp. 1-5

Amirian, E., Liu, Y., Scheurer, M.E., El-Zein, R., Gilbert, M.R. & Bondy, M.L. (2010). Genetic variants in inflammation pathway genes and asthma in glioma susceptibility. *Neuro Oncol*, Vol.12, No.5, pp. 444-452

Bao, G., Wang, M., Guo, S., Han, Y. & Xu, G. (2010). Association between epidermal growth factor +61 G/A polymorphism and glioma risk in a Chinese Han population. *J Int Med Res*, Vol.38, No.5, pp. 1645-1652

Bao, S., Wu, Q., McLendon, R.E., Hao, Y., Shi, Q., Hjelmeland, A.B., Dewhirst, M.W., Bigner, D.D. & Rich, J.N. (2006). Glioma stem cells promote radioresistance by preferential activation of the DNA damage response. *Nature*, Vol.444, No.7120, pp. 756-760

Barcellos-Hoff, M.H., Newcomb, E.W., Zagzag, D. & Narayana, A. (2009). Therapeutic targets in malignant glioblastoma microenvironment. *Semin Radiat Oncol*, Vol.19, No.3, pp. 163-170

Bartek, J. & Lukas, J. (2001). Are all cancer genes equal? *Nature*, Vol.411, No.6841, pp. 1001-1002

Bello, M.J. & Rey, J.A. (2006). The p53/Mdm2/p14ARF cell cycle control pathway genes may be inactivated by genetic and epigenetic mechanisms in gliomas. *Cancer Genet Cytogenet*, Vol.164, No.2, pp. 172-173

Bhowmick, D.A., Zhuang, Z., Wait, S.D. & Weil, R.J. (2004). A functional polymorphism in the EGF gene is found with increased frequency in glioblastoma multiforme patients and is associated with more aggressive disease. *Cancer Res*, Vol.64, No.4, pp. 1220-1223

Bigner, S.H., McLendon, R.E., Fuchs, H., McKeever, P.E. & Friedman, H.S. (1997). Chromosomal characteristics of childhood brain tumors. *Cancer Genet Cytogenet*, Vol.97, No.2, pp. 125-134

Brookes, A.J. (1999). The essence of SNPs. *Gene*, Vol.234, No.2, pp. 177-186

Cairncross, J.G., Ueki, K., Zlatescu, M.C., Lisle, D.K., Finkelstein, D.M., Hammond, R.R., Silver, J.S., Stark, P.C., Macdonald, D.R., Ino, Y., Ramsay, D.A. & Louis, D.N. (1998). Specific genetic predictors of chemotherapeutic response and survival in patients with anaplastic oligodendrogliomas. *J Natl Cancer Inst*, Vol.90, No.19, pp. 1473-1479

Chen, P., Wiencke, J., Aldape, K., Kesler-Diaz, A., Miike, R., Kelsey, K., Lee, M., Liu, J. & Wrensch, M. (2000). Association of an ERCC1 polymorphism with adult-onset glioma. *Cancer Epidemiol Biomarkers Prev*, Vol.9, No.8, pp. 843-847

Cheng, L., Bao, S. & Rich, J.N. (2010). Potential therapeutic implications of cancer stem cells in glioblastoma. *Biochem Pharmacol*, Vol.80, No.5, pp. 654-665

Collins, V.P. (2004). Brain tumours: classification and genes. *J Neurol Neurosurg Psychiatry*, Vol.75 Suppl 2, pp. ii2-11

Conrad, D.F., Jakobsson, M., Coop, G., Wen, X., Wall, J.D., Rosenberg, N.A. & Pritchard, J.K. (2006). A worldwide survey of haplotype variation and linkage disequilibrium in the human genome. *Nat Genet*, Vol.38, No.11, pp. 1251-1260

Costa, B.M., Ferreira, P., Costa, S., Canedo, P., Oliveira, P., Silva, A., Pardal, F., Suriano, G., Machado, J.C., Lopes, J.M. & Reis, R.M. (2007). Association between functional EGF+61 polymorphism and glioma risk. *Clin Cancer Res*, Vol.13, No.9, pp. 2621-2626

Cross, S.H. & Bird, A.P. (1995). CpG islands and genes. *Curr Opin Genet Dev*, Vol.5, No.3, pp. 309-314

Custodio, A.C., Almeida, L.O., Pinto, G.R., Santos, M.J., Almeida, J.R., Clara, C.A., Rey, J.A. & Casartelli, C. (2010). GSTP1 Ile105Val polymorphism in astrocytomas and glioblastomas. *Genet Mol Res*, Vol.9, No.4, pp. 2328-2334

Dang, L., White, D.W., Gross, S., Bennett, B.D., Bittinger, M.A., Driggers, E.M., Fantin, V.R., Jang, H.G., Jin, S., Keenan, M.C., Marks, K.M., Prins, R.M., Ward, P.S., Yen, K.E., Liau, L.M., Rabinowitz, J.D., Cantley, L.C., Thompson, C.B., Vander Heiden, M.G. & Su, S.M. (2009). Cancer-associated IDH1 mutations produce 2-hydroxyglutarate. *Nature*, Vol.462, No.7274, pp. 739-744

Denysenko, T., Gennero, L., Roos, M.A., Melcarne, A., Juenemann, C., Faccani, G., Morra, I., Cavallo, G., Reguzzi, S., Pescarmona, G. & Ponzetto, A. (2010). Glioblastoma cancer stem cells: heterogeneity, microenvironment and related therapeutic strategies. *Cell Biochem Funct*, Vol.28, No.5, pp. 343-351

Dumont, P., Leu, J.I., Della Pietra, A.C., 3rd, George, D.L. & Murphy, M. (2003). The codon 72 polymorphic variants of p53 have markedly different apoptotic potential. *Nat Genet*, Vol.33, No.3, pp. 357-365

Ebert, C., von Haken, M., Meyer-Puttlitz, B., Wiestler, O.D., Reifenberger, G., Pietsch, T. & von Deimling, A. (1999). Molecular genetic analysis of ependymal tumors. NF2 mutations and chromosome 22q loss occur preferentially in intramedullary spinal ependymomas. *Am J Pathol*, Vol.155, No.2, pp. 627-632

Esteller, M., Garcia-Foncillas, J., Andion, E., Goodman, S.N., Hidalgo, O.F., Vanaclocha, V., Baylin, S.B. & Herman, J.G. (2000). Inactivation of the DNA-repair gene MGMT and the clinical response of gliomas to alkylating agents. *N Engl J Med*, Vol.343, No.19, pp. 1350-1354

Franco-Hernandez, C., Martinez-Glez, V., Alonso, M.E., De Campos, J.M., Isla, A., Vaquero, J., Gutierrez, M. & Rey, J.A. (2007). Gene dosage and mutational analyses of EGFR in oligodendrogliomas. *Int J Oncol*, Vol.30, No.1, pp. 209-215

Franco-Hernandez, C., Martinez-Glez, V., de Campos, J.M., Isla, A., Vaquero, J., Gutierrez, M., Casartelli, C. & Rey, J.A. (2009). Allelic status of 1p and 19q in oligodendrogliomas and glioblastomas: multiplex ligation-dependent probe amplification versus loss of heterozygosity. *Cancer Genet Cytogenet*, Vol.190, No.2, pp. 93-96

Felini, M.J., Olshan, A.F., Schroeder, J.C., North, K.E., Carozza, S.E., Kelsey, K.T., Liu, M., Rice, T., Wiencke, J.K. & Wrensch, M.R. (2007). DNA repair polymorphisms XRCC1 and MGMT and risk of adult gliomas. *Neuroepidemiology*, Vol.29, No.1-2, pp. 55-58

Gilbertson, R. (2002). Paediatric embryonic brain tumours. biological and clinical relevance of molecular genetic abnormalities. *Eur J Cancer*, Vol.38, No.5, pp. 675-685

Gilbertson, R.J. & Rich, J.N. (2007). Making a tumour's bed: glioblastoma stem cells and the vascular niche. Nat Rev Cancer, Vol.7, No.10, pp. 733-736

Gonzalez-Gomez, P., Bello, M.J., Arjona, D., Lomas, J., Alonso, M.E., De Campos, J.M., Vaquero, J., Isla, A., Gutierrez, M. & Rey, J.A. (2003). Promoter hypermethylation of multiple genes in astrocytic gliomas. Int J Oncol, Vol.22, No.3, pp. 601-608

Gonzalez-Neira, A., Ke, X., Lao, O., Calafell, F., Navarro, A., Comas, D., Cann, H., Bumpstead, S., Ghori, J., Hunt, S., Deloukas, P., Dunham, I., Cardon, L.R. & Bertranpetit, J. (2006). The portability of tagSNPs across populations: a worldwide survey. *Genome Res*, Vol.16, No.3, pp. 323-330

Gu, J., Liu, Y., Kyritsis, A.P. & Bondy, M.L. (2009). Molecular epidemiology of primary brain tumors. *Neurotherapeutics*, Vol.6, No.3, pp. 427-435

Gutmann, D.H., Donahoe, J., Brown, T., James, C.D. & Perry, A. (2000). Loss of neurofibromatosis 1 (NF1) gene expression in NF1-associated pilocytic astrocytomas. *Neuropathol Appl Neurobiol*, Vol.26, No.4, pp. 361-367

Hanahan, D. & Weinberg, R.A. (2000). The hallmarks of cancer. *Cell*, Vol.100, No.1, pp. 57-70

Harrigan, J.A., Wilson, D.M., 3rd, Prasad, R., Opresko, P.L., Beck, G., May, A., Wilson, S.H. & Bohr, V.A. (2006). The Werner syndrome protein operates in base excision repair and cooperates with DNA polymerase beta. *Nucleic Acids Res*, Vol.34, No.2, pp. 745-754

Hartmann, C., Meyer, J., Balss, J., Capper, D., Mueller, W., Christians, A., Felsberg, J., Wolter, M., Mawrin, C., Wick, W., Weller, M., Herold-Mende, C., Unterberg, A.,

Jeuken, J.W., Wesseling, P., Reifenberger, G. & von Deimling, A. (2009). Type and frequency of IDH1 and IDH2 mutations are related to astrocytic and oligodendroglial differentiation and age: a study of 1,010 diffuse gliomas. *Acta Neuropathol*, Vol.118, No.4, pp. 469-474

Hegi, M.E., Diserens, A.C., Gorlia, T., Hamou, M.F., de Tribolet, N., Weller, M., Kros, J.M., Hainfellner, J.A., Mason, W., Mariani, L., Bromberg, J.E., Hau, P., Mirimanoff, R.O., Cairncross, J.G., Janzer, R.C. & Stupp, R. (2005). MGMT gene silencing and benefit from temozolomide in glioblastoma. *N Engl J Med*, Vol.352, No.10, pp. 997-1003

Herrlinger, U., Rieger, J., Koch, D., Loeser, S., Blaschke, B., Kortmann, R.D., Steinbach, J.P., Hundsberger, T., Wick, W., Meyermann, R., Tan, T.C., Sommer, C., Bamberg, M., Reifenberger, G. & Weller, M. (2006). Phase II trial of lomustine plus temozolomide chemotherapy in addition to radiotherapy in newly diagnosed glioblastoma: UKT-03. *J Clin Oncol*, Vol.24, No.27, pp. 4412-4417

Hofer, S. & Lassman, A.B. (2010). Molecular markers in gliomas: impact for the clinician. *Target Oncol*, Vol.5, No.3, pp. 201-210

Hu, Z., Ma, H., Chen, F., Wei, Q. & Shen, H. (2005). XRCC1 polymorphisms and cancer risk: a meta-analysis of 38 case-control studies. *Cancer Epidemiol Biomarkers Prev*, Vol.14, No.7, pp. 1810-1818

Jakobsson, M., Scholz, S.W., Scheet, P., Gibbs, J.R., VanLiere, J.M., Fung, H.C., Szpiech, Z.A., Degnan, J.H., Wang, K., Guerreiro, R., Bras, J.M., Schymick, J.C., Hernandez, D.G., Traynor, B.J., Simon-Sanchez, J., Matarin, M., Britton, A., van de Leemput, J., Rafferty, I., Bucan, M., Cann, H.M., Hardy, J.A., Rosenberg, N.A. & Singleton, A.B. (2008). Genotype, haplotype and copy-number variation in worldwide human populations. *Nature*, Vol.451, No.7181, pp. 998-1003

Jandial, R., U, H., Levy, M.L. & Snyder, E.Y. (2008). Brain tumor stem cells and the tumor microenvironmen. *Neurosurg Focus*, Vol.24, No.3-4, pp. E27

Jenkins, R.B., Blair, H., Ballman, K.V., Giannini, C., Arusell, R.M., Law, M., Flynn, H., Passe, S., Felten, S., Brown, P.D., Shaw, E.G. & Buckner, J.C. (2006). A t(1;19)(q10;p10) mediates the combined deletions of 1p and 19q and predicts a better prognosis of patients with oligodendroglioma. *Cancer Res*, Vol.66, No.20, pp. 9852-9861

Jones, D.T., Kocialkowski, S., Liu, L., Pearson, D.M., Ichimura, K. & Collins, V.P. (2009). Oncogenic RAF1 rearrangement and a novel BRAF mutation as alternatives to KIAA1549:BRAF fusion in activating the MAPK pathway in pilocytic astrocytoma. *Oncogene*, Vol.28, No.20, pp. 2119-2123

Jones, P.A. & Baylin, S.B. (2007). The epigenomics of cancer. *Cell*, Vol.128, No.4, pp. 683-692

Jones, P.A. & Buckley, J.D. (1990). The role of DNA methylation in cancer. *Adv Cancer Res*, Vol.54, pp. 1-23

Kawabata, M., Kawabata, T. & Nishibori, M. (2005). Role of recA/RAD51 family proteins in mammals. *Acta Med Okayama*, Vol.59, No.1, pp. 1-9

Kiuru, A., Lindholm, C., Heinavaara, S., Ilus, T., Jokinen, P., Haapasalo, H., Salminen, T., Christensen, H.C., Feychting, M., Johansen, C., Lonn, S., Malmer, B., Schoemaker, M.J., Swerdlow, A.J. & Auvinen, A. (2008). XRCC1 and XRCC3 variants and risk of glioma and meningioma. *J Neurooncol*, Vol.88, No.2, pp. 135-142

Kleihues, P. & Cavenee, W.K. (2000). World Health Organisation classification of tumours: Pathology and genetics of tumours of the nervous system. IARC Press, Lyon, France

Kleihues, P., Louis, D.N., Scheithauer, B.W., Rorke, L.B., Reifenberger, G., Burger, P.C. & Cavenee, W.K. (2002). The WHO classification of tumors of the nervous system. *J Neuropathol Exp Neurol*, Vol.61, No.3, pp. 215-225; discussion 226-219

Kleihues, P.; Burger, P.C. & Scheithauer, B.W. (1993). Histological typing of tumours of the central nervous system. World Health Organization international histological classification of tumours. Springer Verlag, Berlin, Heidelberg

Kluwe, L., Hagel, C., Tatagiba, M., Thomas, S., Stavrou, D., Ostertag, H., von Deimling, A. & Mautner, V.F. (2001). Loss of NF1 alleles distinguish sporadic from NF1-associated pilocytic astrocytomas. *J Neuropathol Exp Neurol*, Vol.60, No.9, pp. 917-920

Knudson, A.G., Jr. (1971). Mutation and cancer: statistical study of retinoblastoma. *Proc Natl Acad Sci U S A*, Vol.68, No.4, pp. 820-823

Kobayashi, S., Gibo, H., Sugita, K., Komiya, I. & Yamada, T. (1980). Werner's syndrome associated with meningioma. *Neurosurgery*, Vol.7, No.5, pp. 517-520

Komine, C., Watanabe, T., Katayama, Y., Yoshino, A., Yokoyama, T. & Fukushima, T. (2003). Promoter hypermethylation of the DNA repair gene O6-methylguanine-DNA methyltransferase is an independent predictor of shortened progression free survival in patients with low-grade diffuse astrocytomas. *Brain Pathol*, Vol.13, No.2, pp. 176-184

Korshunov, A., Meyer, J., Capper, D., Christians, A., Remke, M., Witt, H., Pfister, S., von Deimling, A. & Hartmann, C. (2009). Combined molecular analysis of BRAF and IDH1 distinguishes pilocytic astrocytoma from diffuse astrocytoma. *Acta Neuropathol*, Vol.118, No.3, pp. 401-405

Kraus, J.A., de Millas, W., Sorensen, N., Herbold, C., Schichor, C., Tonn, J.C., Wiestler, O.D., von Deimling, A. & Pietsch, T. (2001). Indications for a tumor suppressor gene at 22q11 involved in the pathogenesis of ependymal tumors and distinct from hSNF5/INI1. *Acta Neuropathol*, Vol.102, No.1, pp. 69-74

Krawczak, M., Reiss, J. & Cooper, D.N. (1992). The mutational spectrum of single base-pair substitutions in mRNA splice junctions of human genes: causes and consequences. *Hum Genet*, Vol.90, No.1-2, pp. 41-54

Lamszus, K., Lachenmayer, L., Heinemann, U., Kluwe, L., Finckh, U., Hoppner, W., Stavrou, D., Fillbrandt, R. & Westphal, M. (2001). Molecular genetic alterations on chromosomes 11 and 22 in ependymomas. *Int J Cancer*, Vol.91, No.6, pp. 803-808

Leu, J.I., Dumont, P., Hafey, M., Murphy, M.E. & George, D.L. (2004). Mitochondrial p53 activates Bak and causes disruption of a Bak-Mcl1 complex. *Nat Cell Biol*, Vol.6, No.5, pp. 443-450

Li, X., Dumont, P., Della Pietra, A., Shetler, C. & Murphy, M.E. (2005). The codon 47 polymorphism in p53 is functionally significant. *J Biol Chem*, Vol.280, No.25, pp. 24245-24251

Listernick, R., Charrow, J. & Gutmann, D.H. (1999). Intracranial gliomas in neurofibromatosis type 1. *Am J Med Genet*, Vol.89, No.1, pp. 38-44

Liu, Y., Scheurer, M.E., El-Zein, R., Cao, Y., Do, K.A., Gilbert, M., Aldape, K.D., Wei, Q., Etzel, C. & Bondy, M.L. (2009). Association and interactions between DNA repair

gene polymorphisms and adult glioma. *Cancer Epidemiol Biomarkers Prev*, Vol.18, No.1, pp. 204-214

Liu, Y., Zhang, H., Zhou, K., Chen, L., Xu, Z., Zhong, Y., Liu, H., Li, R., Shugart, Y.Y., Wei, Q., Jin, L., Huang, F., Lu, D. & Zhou, L. (2007). Tagging SNPs in non-homologous end-joining pathway genes and risk of glioma. *Carcinogenesis*, Vol.28, No.9, pp. 1906-1913

Louis, D.N., Ohgaki, H., Wiestler, O.D., Cavenee, W.K., Burger, P.C., Jouvet, A., Scheithauer, B.W. & Kleihues, P. (2007). The 2007 WHO classification of tumours of the central nervous system. *Acta Neuropathol*, Vol.114, No.2, pp. 97-109

Louis, D.N., Pomeroy, S.L. & Cairncross, J.G. (2002). Focus on central nervous system neoplasia. *Cancer Cell*, Vol.1, No.2, pp. 125-128

Macdonald, D.R., Gaspar, L.E. & Cairncross, J.G. (1990). Successful chemotherapy for newly diagnosed aggressive oligodendroglioma. *Ann Neurol*, Vol.27, No.5, pp. 573-574

McCormack, B.M., Miller, D.C., Budzilovich, G.N., Voorhees, G.J. & Ransohoff, J. (1992). Treatment and survival of low-grade astrocytoma in adults--1977-1988. *Neurosurgery*, Vol.31, No.4, pp. 636-642; discussion 642

McKean-Cowdin, R., Barnholtz-Sloan, J., Inskip, P.D., Ruder, A.M., Butler, M., Rajaraman, P., Razavi, P., Patoka, J., Wiencke, J.K., Bondy, M.L. & Wrensch, M. (2009). Associations between polymorphisms in DNA repair genes and glioblastoma. *Cancer Epidemiol Biomarkers Prev*, Vol.18, No.4, pp. 1118-1126

Nakagawachi, T., Soejima, H., Urano, T., Zhao, W., Higashimoto, K., Satoh, Y., Matsukura, S., Kudo, S., Kitajima, Y., Harada, H., Furukawa, K., Matsuzaki, H., Emi, M., Nakabeppu, Y., Miyazaki, K., Sekiguchi, M. & Mukai, T. (2003). Silencing effect of CpG island hypermethylation and histone modifications on O6-methylguanine-DNA methyltransferase (MGMT) gene expression in human cancer. *Oncogene*, Vol.22, No.55, pp. 8835-8844

Natsume, A., Kondo, Y., Ito, M., Motomura, K., Wakabayashi, T. & Yoshida, J. (2010). Epigenetic aberrations and therapeutic implications in gliomas. *Cancer Sci*, Vol.101, No.6, pp. 1331-1336

Ng, H.K. & Lam, P.Y. (1998). The molecular genetics of central nervous system tumors. *Pathology*, Vol.30, No.2, pp. 196-202

Nothnagel, M. & Rohde, K. (2005). The effect of single-nucleotide polymorphism marker selection on patterns of haplotype blocks and haplotype frequency estimates. *Am J Hum Genet*, Vol.77, No.6, pp. 988-998

Nozaki, M., Tada, M., Matsumoto, R., Sawamura, Y., Abe, H. & Iggo, R.D. (1998). Rare occurrence of inactivating p53 gene mutations in primary non-astrocytic tumors of the central nervous system: reappraisal by yeast functional assay. *Acta Neuropathol*, Vol.95, No.3, pp. 291-296

Ohgaki, H. & Kleihues, P. (2005). Epidemiology and etiology of gliomas. *Acta Neuropathol*, Vol.109, No.1, pp. 93-108

Paige, A.J. (2003). Redefining tumour suppressor genes: exceptions to the two-hit hypothesis. *Cell Mol Life Sci*, Vol.60, No.10, pp. 2147-2163

Park, D.M. & Rich, J.N. (2009). Biology of glioma cancer stem cells. *Mol Cells*, Vol.28, No.1, pp. 7-12

Parra, F.C., Amado, R.C., Lambertucci, J.R., Rocha, J., Antunes, C.M. & Pena, S.D. (2003). Color and genomic ancestry in Brazilians. *Proc Natl Acad Sci U S A*, Vol.100, No.1, pp. 177-182

Pinto, G.R., Yoshioka, F.K., Clara, C.A., Santos, M.J., Almeida, J.R., Burbano, R.R., Rey, J.A. & Casartelli, C. (2008a). WRN Cys1367Arg SNP is not associated with risk and prognosis of gliomas in Southeast Brazil. *J Neurooncol*, Vol.90, No.3, pp. 253-258

Pinto, G.R., Yoshioka, F.K., Silva, R.L., Clara, C.A., Santos, M.J., Almeida, J.R., Burbano, R.R., Rey, J.A. & Casartelli, C. (2008b). Prognostic value of TP53 Pro47Ser and Arg72Pro single nucleotide polymorphisms and the susceptibility to gliomas in individuals from Southeast Brazil. *Genet Mol Res*, Vol.7, No.1, pp. 207-216

Reifenberger, G. & Louis, D.N. (2003). Oligodendroglioma: toward molecular definitions in diagnostic neuro-oncology. *J Neuropathol Exp Neurol*, Vol.62, No.2, pp. 111-126

Reifenberger, J., Reifenberger, G., Liu, L., James, C.D., Wechsler, W. & Collins, V.P. (1994). Molecular genetic analysis of oligodendroglial tumors shows preferential allelic deletions on 19q and 1p. *Am J Pathol*, Vol.145, No.5, pp. 1175-1190

Reya, T., Morrison, S.J., Clarke, M.F. & Weissman, I.L. (2001). Stem cells, cancer, and cancer stem cells. *Nature*, Vol.414, No.6859, pp. 105-111

Richardson, B. (2003). Impact of aging on DNA methylation. *Ageing Res Rev*, Vol.2, No.3, pp. 245-261

Riemenschneider, M.J., Jeuken, J.W., Wesseling, P. & Reifenberger, G. (2010). Molecular diagnostics of gliomas: state of the art. *Acta Neuropathol*, Vol.120, No.5, pp. 567-584

Rivera, A.L., Pelloski, C.E., Gilbert, M.R., Colman, H., De La Cruz, C., Sulman, E.P., Bekele, B.N. & Aldape, K.D. (2010). MGMT promoter methylation is predictive of response to radiotherapy and prognostic in the absence of adjuvant alkylating chemotherapy for glioblastoma. *Neuro Oncol*, Vol.12, No.2, pp. 116-121

Rush, L.J. & Plass, C. (2002). Alterations of DNA methylation in hematologic malignancies. *Cancer Lett*, Vol.185, No.1, pp. 1-12

Ryberg, D., Skaug, V., Hewer, A., Phillips, D.H., Harries, L.W., Wolf, C.R., Ogreid, D., Ulvik, A., Vu, P. & Haugen, A. (1997). Genotypes of glutathione transferase M1 and P1 and their significance for lung DNA adduct levels and cancer risk. *Carcinogenesis*, Vol.18, No.7, pp. 1285-1289

Sachidanandam, R., Weissman, D., Schmidt, S.C., Kakol, J.M., Stein, L.D., Marth, G., Sherry, S., Mullikin, J.C., Mortimore, B.J., Willey, D.L., Hunt, S.E., Cole, C.G., Coggill, P.C., Rice, C.M., Ning, Z., Rogers, J., Bentley, D.R., Kwok, P.Y., Mardis, E.R., Yeh, R.T., Schultz, B., Cook, L., Davenport, R., Dante, M., Fulton, L., Hillier, L., Waterston, R.H., McPherson, J.D., Gilman, B., Schaffner, S., Van Etten, W.J., Reich, D., Higgins, J., Daly, M.J., Blumenstiel, B., Baldwin, J., Stange-Thomann, N., Zody, M.C., Linton, L., Lander, E.S. & Altshuler, D. (2001). A map of human genome sequence variation containing 1.42 million single nucleotide polymorphisms. *Nature*, Vol.409, No.6822, pp. 928-933

Salisbury, B.A., Pungliya, M., Choi, J.Y., Jiang, R., Sun, X.J. & Stephens, J.C. (2003). SNP and haplotype variation in the human genome. *Mutat Res*, Vol.526, No.1-2, pp. 53-61

Salomon, D.S., Brandt, R., Ciardiello, F. & Normanno, N. (1995). Epidermal growth factor-related peptides and their receptors in human malignancies. *Crit Rev Oncol Hematol*, Vol.19, No.3, pp. 183-232

Sanoudou, D., Tingby, O., Ferguson-Smith, M.A., Collins, V.P. & Coleman, N. (2000). Analysis of pilocytic astrocytoma by comparative genomic hybridization. *Br J Cancer*, Vol.82, No.6, pp. 1218-1222

Sanson, M., Marie, Y., Paris, S., Idbaih, A., Laffaire, J., Ducray, F., El Hallani, S., Boisselier, B., Mokhtari, K., Hoang-Xuan, K. & Delattre, J.Y. (2009). Isocitrate dehydrogenase 1 codon 132 mutation is an important prognostic biomarker in gliomas. *J Clin Oncol*, Vol.27, No.25, pp. 4150-4154

Schuebel, K.E., Chen, W., Cope, L., Glockner, S.C., Suzuki, H., Yi, J.M., Chan, T.A., Van Neste, L., Van Criekinge, W., van den Bosch, S., van Engeland, M., Ting, A.H., Jair, K., Yu, W., Toyota, M., Imai, K., Ahuja, N., Herman, J.G. & Baylin, S.B. (2007). Comparing the DNA hypermethylome with gene mutations in human colorectal cancer. *PLoS Genet*, Vol.3, No.9, pp. 1709-1723

Schwartzbaum, J., Ahlbom, A., Malmer, B., Lonn, S., Brookes, A.J., Doss, H., Debinski, W., Henriksson, R. & Feychting, M. (2005). Polymorphisms associated with asthma are inversely related to glioblastoma multiforme. *Cancer Res*, Vol.65, No.14, pp. 6459-6465

Shahbazi, M., Pravica, V., Nasreen, N., Fakhoury, H., Fryer, A.A., Strange, R.C., Hutchinson, P.E., Osborne, J.E., Lear, J.T., Smith, A.G. & Hutchinson, I.V. (2002). Association between functional polymorphism in EGF gene and malignant melanoma. *Lancet*, Vol.359, No.9304, pp. 397-401

Shete, S., Hosking, F.J., Robertson, L.B., Dobbins, S.E., Sanson, M., Malmer, B., Simon, M., Marie, Y., Boisselier, B., Delattre, J.Y., Hoang-Xuan, K., El Hallani, S., Idbaih, A., Zelenika, D., Andersson, U., Henriksson, R., Bergenheim, A.T., Feychting, M., Lonn, S., Ahlbom, A., Schramm, J., Linnebank, M., Hemminki, K., Kumar, R., Hepworth, S.J., Price, A., Armstrong, G., Liu, Y., Gu, X., Yu, R., Lau, C., Schoemaker, M., Muir, K., Swerdlow, A., Lathrop, M., Bondy, M. & Houlston, R.S. (2009). Genome-wide association study identifies five susceptibility loci for glioma. *Nat Genet*, Vol.41, No.8, pp. 899-904

Simpson, J.R., Horton, J., Scott, C., Curran, W.J., Rubin, P., Fischbach, J., Isaacson, S., Rotman, M., Asbell, S.O., Nelson, J.S. & et al. (1993). Influence of location and extent of surgical resection on survival of patients with glioblastoma multiforme: results of three consecutive Radiation Therapy Oncology Group (RTOG) clinical trials. *Int J Radiat Oncol Biol Phys*, Vol.26, No.2, pp. 239-244

Smith, J.S., Perry, A., Borell, T.J., Lee, H.K., O'Fallon, J., Hosek, S.M., Kimmel, D., Yates, A., Burger, P.C., Scheithauer, B.W. & Jenkins, R.B. (2000). Alterations of chromosome arms 1p and 19q as predictors of survival in oligodendrogliomas, astrocytomas, and mixed oligoastrocytomas. *J Clin Oncol*, Vol.18, No.3, pp. 636-645

Sreeja, L., Syamala, V.S., Syamala, V., Hariharan, S., Raveendran, P.B., Vijayalekshmi, R.V., Madhavan, J. & Ankathil, R. (2008). Prognostic importance of DNA repair gene polymorphisms of XRCC1 Arg399Gln and XPD Lys751Gln in lung cancer patients from India. *J Cancer Res Clin Oncol*, Vol.134, No.6, pp. 645-652

Stiles, C.D. & Rowitch, D.H. (2008). Glioma stem cells: a midterm exam. *Neuron*, Vol.58, No.6, pp. 832-846

Sugimura, T. & Ushijima, T. (2000). Genetic and epigenetic alterations in carcinogenesis. *Mutat Res*, Vol.462, No.2-3, pp. 235-246

Syamala, V.S., Sreeja, L., Syamala, V., Raveendran, P.B., Balakrishnan, R., Kuttan, R. & Ankathil, R. (2008). Influence of germline polymorphisms of GSTT1, GSTM1, and GSTP1 in familial versus sporadic breast cancer susceptibility and survival. *Fam Cancer*, Vol.7, No.3, pp. 213-220

Taylor, J.G., Choi, E.H., Foster, C.B. & Chanock, S.J. (2001). Using genetic variation to study human disease. *Trends Mol Med*, Vol.7, No.11, pp. 507-512

Urioste, M., Martinez-Ramirez, A., Cigudosa, J.C., Colmenero, I., Madero, L., Robledo, M., Martinez-Delgado, B. & Benitez, J. (2002). Complex cytogenetic abnormalities including telomeric associations and MEN1 mutation in a pediatric ependymoma. *Cancer Genet Cytogenet*, Vol.138, No.2, pp. 107-110

Vauleon, E., Auger, N., Benouaich-Amiel, A., Laigle-Donadey, F., Kaloshi, G., Lejeune, J., Delattre, J.Y., Thillet, J. & Sanson, M. (2007). The 61 A/G EGF polymorphism is functional but is neither a prognostic marker nor a risk factor for glioblastoma. *Cancer Genet Cytogenet*, Vol.172, No.1, pp. 33-37

Visvader, J.E. & Lindeman, G.J. (2008). Cancer stem cells in solid tumours: accumulating evidence and unresolved questions. *Nat Rev Cancer*, Vol.8, No.10, pp. 755-768

Vogelstein, B. & Kinzler, K.W. (2004). Cancer genes and the pathways they control. *Nat Med*, Vol.10, No.8, pp. 789-799

von Haken, M.S., White, E.C., Daneshvar-Shyesther, L., Sih, S., Choi, E., Kalra, R. & Cogen, P.H. (1996). Molecular genetic analysis of chromosome arm 17p and chromosome arm 22q DNA sequences in sporadic pediatric ependymomas. *Genes Chromosomes Cancer*, Vol.17, No.1, pp. 37-44

Wang, L.E., Bondy, M.L., Shen, H., El-Zein, R., Aldape, K., Cao, Y., Pudavalli, V., Levin, V.A., Yung, W.K. & Wei, Q. (2004). Polymorphisms of DNA repair genes and risk of glioma. *Cancer Res*, Vol.64, No.16, pp. 5560-5563

Wang, S., Zhao, Y., Ruan, Z., Chen, H., Fan, W., Chen, J., Wu, Q., Qian, J., Zhang, T., Huang, Y. & Lu, D. (2010). Association between EGF +61 G/A and glioma risk in a Chinese population. *BMC Cancer*, Vol.10, pp. 221

White, D.L., Li, D., Nurgalieva, Z. & El-Serag, H.B. (2008). Genetic variants of glutathione S-transferase as possible risk factors for hepatocellular carcinoma: a HuGE systematic review and meta-analysis. *Am J Epidemiol*, Vol.167, No.4, pp. 377-389

Wick, W., Hartmann, C., Engel, C., Stoffels, M., Felsberg, J., Stockhammer, F., Sabel, M.C., Koeppen, S., Ketter, R., Meyermann, R., Rapp, M., Meisner, C., Kortmann, R.D., Pietsch, T., Wiestler, O.D., Ernemann, U., Bamberg, M., Reifenberger, G., von Deimling, A. & Weller, M. (2009). NOA-04 randomized phase III trial of sequential radiochemotherapy of anaplastic glioma with procarbazine, lomustine, and vincristine or temozolomide. *J Clin Oncol*, Vol.27, No.35, pp. 5874-5880

Wrensch, M., Jenkins, R.B., Chang, J.S., Yeh, R.F., Xiao, Y., Decker, P.A., Ballman, K.V., Berger, M., Buckner, J.C., Chang, S., Giannini, C., Halder, C., Kollmeyer, T.M., Kosel, M.L., LaChance, D.H., McCoy, L., O'Neill, B.P., Patoka, J., Pico, A.R., Prados, M., Quesenberry, C., Rice, T., Rynearson, A.L., Smirnov, I., Tihan, T., Wiemels, J., Yang, P. & Wiencke, J.K. (2009). Variants in the CDKN2B and RTEL1 regions are associated with high-grade glioma susceptibility. *Nat Genet*, Vol.41, No.8, pp. 905-908

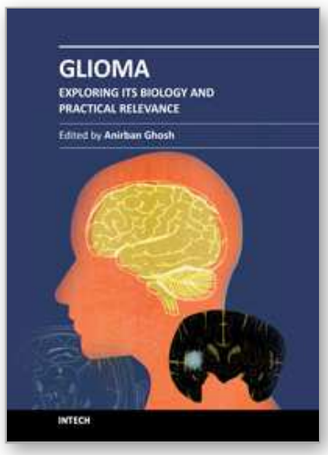
Wrensch, M., Kelsey, K.T., Liu, M., Miike, R., Moghadassi, M., Sison, J.D., Aldape, K., McMillan, A., Wiemels, J. & Wiencke, J.K. (2005). ERCC1 and ERCC2 polymorphisms and adult glioma. *Neuro Oncol*, Vol.7, No.4, pp. 495-507

Yan, H., Parsons, D.W., Jin, G., McLendon, R., Rasheed, B.A., Yuan, W., Kos, I., Batinic-Haberle, I., Jones, S., Riggins, G.J., Friedman, H., Friedman, A., Reardon, D., Herndon, J., Kinzler, K.W., Velculescu, V.E., Vogelstein, B. & Bigner, D.D. (2009). IDH1 and IDH2 mutations in gliomas. *N Engl J Med*, Vol.360, No.8, pp. 765-773

Zattara-Cannoni, H., Gambarelli, D., Lena, G., Dufour, H., Choux, M., Grisoli, F. & Vagner-Capodano, A.M. (1998). Are juvenile pilocytic astrocytomas benign tumors? A cytogenetic study in 24 cases. *Cancer Genet Cytogenet*, Vol.104, No.2, pp. 157-160

Zhu, Y. & Parada, L.F. (2002). The molecular and genetic basis of neurological tumours. *Nat Rev Cancer*, Vol.2, No.8, pp. 616-626

Zülch, K.J. (1979). Histologic typing of tumours of the central nervous system. World Health Organization, Geneva, Switzerland



Glioma - Exploring Its Biology and Practical Relevance

Edited by Dr. Anirban Ghosh

ISBN 978-953-307-379-8
Hard cover, 486 pages
Publisher InTech
Published online 02, November, 2011
Published in print edition November, 2011

The tittle 'Glioma - Exploring Its Biology and Practical Relevance' is indicative of its content. This volume contains 21 chapters basically intended to explore glioma biology and discussing the experimental model systems for the purpose. It is hoped that the present volume will provide supportive and relevant awareness and understanding on the fundamental advances of the subject to the professionals from any sphere interested about glioma.

How to reference

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Giovanny Pinto, France Yoshioka, Fábio Motta, Renata Canalle, Rommel Burbano, Juan Rey, Aline Custódio and Cacilda Casartelli (2011). Genomic Abnormalities in Gliomas, Glioma - Exploring Its Biology and Practical Relevance, Dr. Anirban Ghosh (Ed.), ISBN: 978-953-307-379-8, InTech, Available from: http://www.intechopen.com/books/glioma-exploring-its-biology-and-practical-relevance/genomic-abnormalities-in-gliomas

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