Chapter 3

MOLECULAR GENETICS OF BRAIN TUMORS

Kyriakos Papadimitriou, Chetan Bettegowda and Frank Vrionis

1 Department of Neurosurgery, Johns Hopkins University, Baltimore, MD
2 Department of NeuroOncology H. Lee Moffitt Cancer Center and Research Institute and Department of Neurosurgery, University of South Florida, Tampa, FL, US

ABSTRACT

Alterations in a brain cell genome, within genes that control cell growth, cell cycle, and cell death, are the basis for the formation of brain tumors. These mutations usually arise spontaneously during cell division or as a result of failure to properly correct DNA damage. External causes may significantly increase the risk for development of a brain tumor; yet this evidence regarding this malignancy remains limited. In this chapter, the identified gene alterations that are implicated in the development of a brain cancer are reviewed. However, further research is of significant importance to acquire a complete picture of the various gene mutation patterns for each cancer.

INTRODUCTION

The genetic understanding of brain tumors has substantially increased over the last several years. The basic principle of tumorigenesis is that cells accumulate DNA alterations and damage that as a result mutations of critical genes that then allows for uncontrolled cell division. A normal cell will tightly regulate cell replication but a cancer cell has uncontrolled growth driven by pathologic instructions from the mutated genome. Normally, cells are driven to maintain homeostasis with the surrounding environment, whereas cancer cell will invade and eventually destroy the surrounding brain.

Although for a small percentage of brain tumors the first mutation is inherited as part of a hereditary syndrome such as Von Hippel Lindaeu, in most tumors mutations arise spontaneously during cell division and/or as a result of improper DNA repair. In both

* E-mail: Frank.Vrionis@moffitt.org
scenarios subsequent mutations are needed to initiate tumor formation. According to Knudson theory, the first hit dramatically increases the risk of tumor formation, but by itself it is not sufficient. The paradigm for hereditary cancer syndromes involves the inheritance of a mutation in a tumor suppressor gene in the germline and a second spontaneous mutation inactivating the remaining allele.

The way to distinguish a somatic from a hereditary mutation is to sequence the suspected gene mutation in both the tumor and normal tissue, such as lymphocyte DNA. If the mutation is detected only in the tumor sample and not in normal tissue, it is evidence for a somatic mutation. Neurofibromatosis type 1, Li-Fraumani Syndrome, familial adenomatous polyposis are examples of syndromes that are associated with inherited tumor suppressor gene mutation.

**Tumor Suppressors, Oncogenes and Mutator Genes**

Gene mutations that are associated with tumorigenesis can be classified by how the mutation contributes to tumor formation. Two main categories exist: Gain or loss of function. Gain of function mutations are activating and convert a proto-oncogene to an oncogene. Activation of only one allele of an oncogene can contribute functionally to tumor progression in concert with other gene mutations. Several mechanisms of proto-oncogene activation have been proposed, such as amplification, splicing-related mutations that add or delete gene exons and point mutations that increase activity of the protein.

Loss of function mutations are typically associated with tumor suppressor genes. These genes function as genome guardians and they normally prevent malignant transformation. Missense or non-sense mutations, deletions or insertions can render the protein non-functional.

Lastly, mutator genes (i.e. DNA repair enzymes) can increase the mutation rate in the cell’s DNA. When DNA repair enzymes are altered due to inactivating mutations, the cell subsequently loses its ability to adequately repair errors that occur during DNA replication. The increased rate of DNA mutations then can lead to critical changes in oncogenes and tumor suppressor genes. For instance, in GBMs about 5% of tumors will have dysfunction of the mismatch repair enzymes machinery.

**Mutations that Underlie Brain Tumors**

With the completion of the human genome project and the advent of next generation sequencing technology, genome wide genetic studies are now feasible. One of the key principles from these landmark studies is that the number and combination of mutations that can be used by the cancer cell to escape the normal control mechanism are far larger and more complex than originally envisioned by scientists.

One such global sequencing study is from Parson et al. [1] who studied 22 glioblastoma samples. They sequenced 20,661 protein coding genes in order to determine the presence of alterations within the coding regions of the genome. In addition, amplifications and deletions were detected using high-density oligonucleotide arrays and gene expression analyses were performed to correlate genetic changes to mRNA levels. This study revealed that some of the
pathways known to be altered in GBMs affect a larger fraction of genes and patients than previously anticipated. A majority of the tumors analyzed had alterations in genes encoding components of each of the TP53, RB1, and PI3K pathways. The comprehensive nature of their study led to the identification of IDH1 as an unexpected target of genetic alteration in 5 patients with GBM. All mutations in this gene resulted in amino acid substitutions at position 132. All 5 had the same heterozygous point mutation, a change of a guanine to an adenine at position 395 of the IDH1 transcript (G395A), leading to the replacement of an arginine with a histidine at amino acid residue 132 of the protein (R132H).

**GLIOBLASTOMAS**

Glioblastoma multiforme (GBM) is the most common and lethal type of brain cancer [1] and therefore the genetic basis for this disease has been better characterized than for other central nervous system neoplasms. They are classified as grade I to grade IV on the basis of histopathological and clinical criteria established by the World Health Organization (WHO) [2]. Historically, GBMs have been categorized into two groups “primary” and “secondary” [3] on the basis of clinical presentation. Primary GBMs first occur as a grade IV tumor, whereas secondary GBMs are defined as cancers that have clinical, radiologic, or histopathologic evidence of malignant progression from a preexisting lower-grade tumor [3].

Substantial research effort has focused on the identification of genetic alterations in GBMs that might help define subclasses of GBM patients with differing prognoses and responses to specific therapies [1]. For example, distinctions between the genetic lesions found in primary and secondary GBMs have been made. TP53 mutation appear to be a relatively early event during the development of an astrocytoma, whereas the loss or mutation of PTEN and amplification of EGFR are characteristic of higher-grade tumors. Specifically, secondary GBMs have a higher frequency of TP53 alterations rather than primary; 65% versus 28%, lower frequency of PTEN mutation; 4% versus 25% and lower rate of EGFR amplification 8% versus 36% [4-6]. It has been reported that the types of TP53 mutations differ between primary and secondary GBMs. In the first population-based study on glioblastomas that includes incidence, survival rates, and key genetic alterations by Oghaki et al. [7], in 57% of secondary glioblastomas the mutations were located in the two-hotspot codons, 248 and 273. In primary glioblastomas, mutations were more equally distributed through exons, only 17% occurring in codons 248 and 273.

Glioblastomas cell lines have been the historical standard both for exploring the biology of human tumors and as preclinical models for screening potential therapeutic agents [8]. It has become increasingly clear, however, that phenotypic characteristics and the multitude of genetic aberrations found within repeatedly in vitro passaged cancer cell lines often bear little resemblance to those found within the corresponding primary human tumor [8]. The concept of tumor stem cells (TSCs) provides a new paradigm for understanding tumor biology, although it remains unclear whether TSCs will prove to be a more robust model than traditional cancer cell lines. TSCs may be a more reliable model than many commonly utilized cancer cell lines for understanding the biology of primary human tumors [8]. By using a model system derived from primary GBMs, it has been demonstrated that NBE-
cultured ("NBE" conditions: serum free Neurobasal media supplemented with basic FGF and EGF) cells derived from primary GBMs bear remarkable similarity to normal NSCs.

In a screening of 20,661 genes, 5 out of 22 GBMs tumors had the same heterozygous point mutation, a change of a guanine to an adenine at position 395 of the IDH1 transcript (G395A), leading to the replacement of an arginine with a histidine at amino acid residue 132 of the protein (R132H) [1]. The mutation in IDH1 preferentially occurs in younger GBM patients, with a mean age of 33 years for IDH1-mutated patients, as opposed to 53 years for patients with wild-type IDH1 (P < 0.001, t test). Interestingly, mutations in IDH1 are found in nearly all of the patients with secondary GBMs (mutations in 5 of 6 secondary GBM patients, as compared to 7 of 99 patients with primary GBMs) (P < 0.001, binomial test). Lastly, patients with IDH1 mutations have a significantly improved prognosis, with a median overall survival of 3.8 years as compared to 1.1 years for patients with wild-type IDH1.

To assess the enzymatic activity of wild-type and mutant IDH1 and IDH2 proteins, Yan et al. utilized a human oligodendroglioma line without IDH1 or IDH2 mutations that was transfected with a vector containing the coding sequences of the wild-type IDH1, wild-type IDH2, or mutant IDH genes (corresponding to the most common IDH1 mutation, R132H, or the IDH2 mutations R172G, R172K, and R172M) [2]. They measured the enzymatic activity (reduction of NADP+ to NADPH) of IDH1 and IDH2 proteins in an oligodendroglioma line that had been transfected with wild-type or mutant IDH1 or IDH2 genes. These mutants represented 88% of the IDH1 mutations and 100% of the IDH2 mutations found in patients. Data showed that exogenous expression of wild-type IDH1 or IDH2 significantly increased the production of NADPH, whereas only endogenous IDH activity was observed in cells that had been transfected with mutant IDH1 or IDH2 genes. Wild-type (WT) IDH1 converts isocitrate and NADP+ to α-ketoglutarate (α-KG) and NADPH. Mutated amino acids in IDH1 and IDH2 reside in the catalytic pocket and result in a neo-enzymatic activity: α-KG + NADPH → D-2-hydroxyglutarate (2-HG) + NADP+. Although the role of IDH1 mutation in tumorigenesis has not been determined, decreased NADPH production from loss of IDH1 WT function coupled with increased 2-HG levels could lead to oxidative stress. Furthermore, 2-HG interferes with the electron transport chain and could alter mitochondrial physiology and drive cells toward aerobic glycolysis [9-11].

Mutations that arise during tumorigenesis may provide a selective advantage to the tumor cell (driver mutations) or have no net effect on tumor growth (passenger mutations). Identification of GBM candidate cancer genes (CAN-genes) are worth further investigation since they are most likely drivers. The CAN-genes reported in the literature include TP53, PTEN, CDKN2A, RB1, EGFR, NF1, PIK3CA, and PIK3R1. Of these genes, the most frequently altered are CDKN2A (altered in 50% of GBMs); TP53, EGFR, and PTEN (altered in 30 to 40%); NF1, CDK4, and RB1 (altered in 12 to 15%); and PIK3CA and PIK3R1 (altered in 8 to 10%).

The phosphatidylinositol 3-kinases (PI3K) are a family of enzymes that relay important cellular growth control signals. In half of GBMs there is either a PI3K-activating mutation or a deletion/mutation of its negative regulator PTEN. A mutated insulin-mediated activator of PI3K kinase, insulin substrate receptor-1 has also been reported [12]. This observation is confirmed in a study by Gallia et al. [12]. The authors found that this mutation occurs in a significant number of human glioblastomas, further indicating that therapeutic targeting of this pathway in glioblastomas is of value. Moreover, PIK3CA mutations are identified in 21% of pediatric primary glioblastomas and in 17% of adult patients.
The PTEN gene importantly encodes a protein that regulates cell proliferation, apoptosis, and tumor invasion. PTEN mutations have been reported in 15% to 40% of glioblastomas [4, 13]. Most missense mutations are located in exons 1 to 6, the region homologous to tensin, auxilin, and dual-specificity phosphatases, whereas nonsense mutations and deletions or insertions leading to stop codons and protein truncation are located more evenly throughout the gene. In several studies, PTEN mutations were not associated with prognosis of glioblastoma patients, and this was confirmed at the population level [7].

One important gene that deserves special attention is the EGFR, as is genomically amplified in 40% of tumors [14]. After genomic amplification, the EGFR gene may undergo further rearrangement. The most frequently identified deletion, is loss of the internal exons that correspond to the coding sequence for amino acids 6 to 273 [15]. This is referred to as the EGFR type 3 rearrangement, or EGVRvIII [16]. In another study, the authors show that this common activating epidermal growth factor receptor (EGFR) mutation (EGFRvIII) stimulates mTORC2 kinase activity, which is partially suppressed by PTEN. The mTORC2 signaling promotes GBM growth and survival, and activates NF-κB. Importantly, this mTORC2-NF-κB pathway renders GBM cells resistant to chemotherapy in a manner independent of Akt [17]. The predictive value of EGFR amplification has been unclear. Studies have reported that EGFR amplification is a significant predictor of poorer overall survival in glioblastoma patients and that the EGFR gene status is a more significant prognostic factor in younger patients [18]. Other studies found EGFR amplification to be a predictor of longer survival in older glioblastoma patients [19].

Data on the predictive value of TP53 mutations in glioblastomas have been contradictory. While some hospital-based studies showed no association between TP53 status and outcome of glioblastoma patients [20], one study showed that the presence of TP53 mutations was a favorable prognostic factor [21]. In another study however, age-adjusted multivariate analysis revealed no difference in survival between patients with and without TP53 mutations [7].

In a recent comprehensive study, cancer-specific DNA methylation of CpG dinucleotides located in CpG islands within the promoters of 2,305 genes were measured relative to normal brain [22]. The promoter methylation status of MGMT, a DNA repair enzyme that removes alkyl groups from guanine residues, is associated with GBM sensitivity to alkylating agents. Twenty-one percent of the cases were found to contain MGMT promoter methylation [22]. Among the treated samples lacking MGMT methylation (29%) of the validated somatic mutations occurred as G:C to A:T transitions in CpG dinucleotides (characteristic of spontaneous deamination of methylated cytosines), and a comparable 23% of all mutations occurred as G:C to A:T transitions in non-CpG dinucleotides. In contrast, in the treated samples with MGMT methylation, 81% of all mutations turned out to be of the G:C to A:T transition type in non-CpG dinucleotides whereas only 4% of all mutations were G:C to A:T transition mutations within CpGs. That pattern is consistent with a failure to repair alkylated guanine residues caused by treatment. In other words, MGMT methylation shifted the mutation spectrum of treated samples to a preponderance of G:C to A:T transition at non-CpG sites [22].

In a previously described study [22], all seven mutations in Mismatch repair (MMR) genes found in six MGMT methylated hypermutated (treated) tumors occurred as G:C to A:T mutations at non-CpG sites. No MMR mutations in nonmethylated hypermutated tumors had this characteristic. Therefore, MMR deficiency and MGMT methylation together, in the context of treatment, exert a powerful influence on the overall frequency and pattern of
somatic point mutations in GBM tumors [22]. Microsatellite instability (MSI) has been identified in various human cancers, particularly those associated with the hereditary nonpolyposis colorectal cancer syndrome (HNPCC). Although gliomas have been reported in a few hereditary nonpolyposis colorectal cancer syndromes, data on the incidence of MSI in gliomas are conflicting, and the nature of the mismatch repair defect is not entirely known [23]. Five percent of GBMs have microsatellite instability, a sign of functional MMR mutation. This mutation is more commonly identified in relapsing patients and is associated with rapid acquisition of drug resistance [24, 25].

The link between age and genetic alterations in glioblastomas has been investigated in the literature. Glioblastomas with a TP53 mutation were observed in younger patients (mean: 53 years), in particular in patients younger than 35 years [4]. The mean age of patients with glioblastomas carrying a PTEN mutation and LOH 10q were older than those without these alterations. Interestingly, EGFR amplification was never observed in any glioblastoma that developed in patients below 35 years of age [4]. Hence, the poor prognosis of older patients cannot be explained by the frequency of specific genetic alterations or the combination.

**LOW-GRADE ASTROCYTOMAS AND OLIGODENDROGLIOMAS**

Low-grade gliomas, defined by the World Health Organization (WHO) as grade I or II oligodendroglioma, astrocytoma, or mixed oligoastrocytoma, accounts for about 10% of all primary central nervous system tumors and 25% of gliomas [26]. Because WHO grades I–II gliomas are significantly less common than high-grade gliomas, availability of tissue for histologic and molecular analysis has made such investigations more difficult than similar research for high-grade gliomas. Although most low-grade gliomas are relatively slow-growing, they can behave heterogeneously, and therefore outcomes vary widely. Surgical resection is the primary modality of treatment, and the role of adjuvant radiation therapy remains controversial. Although at a higher rate, the TP53 mutations are found in grade II astrocytomas similar to GBMs. TP53 mutations were most frequent in gemistocytic astrocytomas (88%), followed by fibrillary astrocytomas and oligoastrocytomas, but infrequent (13%) in oligodendrogliomas [4].

Pilocytic astrocytomas are the most frequent brain tumor affecting children. They are classified as grade I astrocytomas by the World Health Organization (WHO). They occur predominantly in children and have a better prognosis than higher-grade astrocytomas, with a 10-year survival rate as high as 96% [4]. This tumor is usually not infiltrating and progression to higher grades occurs in less than 20% of the patients. Although gross total resection may result in cure, recurrence is seen in 19% of cases [27]. Recent studies highlight the importance of BRAF alterations resulting in mitogen activated protein kinase (MAK/ERK) pathway activation in low-grade CNS tumors [28]. For this purpose, Lin et al. studied 106 low-grade CNS neoplasms in a cohort of primarily pediatric patients to identify the prevalence and clinicopathologic significance of these alterations [28]. They found that BRAF alterations included KIAA1549:BRAF fusions in 51 (48%) and BRAF exon 15 (BRAF V600E) point mutations in 8 (8%). These alterations were more common in tumors arising from the cerebellum and optic pathways.
Oligodendroglioma, is a glioma subtype marked by unique clinical, pathological, and genetic characteristics. Unlike other gliomas such as astrocytomas and ependymomas, oligodendrogliomas are chemosensitive and often progress in a slow and predictable manner [29]. They display a classical appearance of cells, with round, regular nuclei associated with clearing of the cytoplasm and in close proximity to fine branching vasculature.

Oligodendrogliomas are the second most common malignant brain tumor in adults and often exhibit characteristic losses of chromosomes 1p and 19q [30]. They account for 20% of brain tumors in adults and, as their name implies, they consist primarily of cells resembling oligodendroglia [31]. To date, the best biomarker for oligodendrogliomas is loss of heterozygosity (LOH) of chromosomes 1p and 19q. Assessment for LOH events is now commonly performed in patients with oligodendrogliomas because of their important implications for therapeutic responses [30, 32, 33]. The chromosome losses occur in 50% to 70% of tumors and are often associated with a pericentromeric translocation of chromosomes 1 and 19, producing marker chromosome der (1;19) (q10;p10). This translocation is unbalanced, leaving the cells with one copy of the short arm of chromosome 1 and one copy of the long arm of chromosome 19. This suggests that the basis for the t (1;19) translocation is the unmasking of a tumor suppressor gene(s) on either chromosome 1p or 19q.

Recently, Bettegowda and colleagues performed exomic sequencing of seven tumors with 1p/19q co-deletion in order to better understand the biologic basis of the der (1;19) (q10;p10) translocation. The authors found that the CIC gene on chromosome 19q was somatically mutated in six cases and that the FUBP1 gene [encoding far upstream element (FUSE) binding protein] on chromosome 1p was somatically mutated in two tumors. Further examination of 27 additional oligodendrogliomas revealed 12 and 3 more tumors with mutations of CIC and FUBP1, respectively. The vast majority of mutations in these two genes were predicted to inactivate function of the proteins, suggesting that both act as tumor suppressor genes. One compelling possibility is that 1p/19q co-deletion is a mechanism of inactivating one copy of these tumor suppressor genes. The second copy could then be inactivated via other epigenetic or genetic mechanisms. Furthermore, the loss of 1p/19q in oligodendrogliomas accurately predicts sensitivity to chemotherapy [34, 35]. It remains to what role CIC and FUBP1 play in conferring this chemosensitivity.

In addition, oligodendrogliomas are associated with a constellation of positive prognostic markers including methylation of the MGMT promoter, IDH1 mutations, and the recently described CpG island methylator phenotype (G-CIMP) [36]. These markers are also present in glioblastomas that arise from low-grade astrocytomas. An important divergence in the molecular pathogenesis of low-grade oligodendrogliomas and astrocytomas is 1p/19q co-deletion in the former and TP53 mutations in the latter. The mutual exclusivity of these events underscores the distinct molecular characteristics of oligodendrogliomas [29]. These findings indicate that LOH 1p/19q and TP53 mutations are genetic alterations that clearly distinguish two pathways leading to oligodendrogliomas and to low-grade astrocytomas, respectively [4].

TP53 mutations are significantly more frequent in secondary than primary glioblastomas. In the pathway leading to secondary glioblastomas, TP53 mutations are early genetic events, since they are already present in low-grade and anaplastic gliomas at similar frequencies, while LOH 10q is a late genetic event [4]. It is intriguing that recurrent mutation in CIC, located on chromosome 19q, is found almost exclusively in 1p/19q co-deleted oligodendrogliomas with IDH1 mutation, yet loss of chromosome 1p is more strongly
associated with the oligodendrogliomatous phenotype and clinical behavior than 19q loss [35].

**MEDULLOBLASTOMAS**

Medulloblastomas are the most common malignant brain tumor of children [37]. Medulloblastomas arise in the cerebellum, have a propensity to disseminate throughout the central nervous system, and are diagnosed in approximately 1 in 200,000 children less than 15 years old each year [37]. Over the last 30 years, medulloblastoma has been the subject of a number of studies undertaken to improve the disease’s prognosis by combining chemotherapy with postoperative radiotherapy [38]. Although aggressive multimodal therapy has improved the prognosis for children with medulloblastomas, a significant proportion of patients are currently incurable [39].

Moreover, survivors often suffer significant treatment-related morbidities, including neurocognitive deficits related to radiation therapy. The benefit in terms of limited neuropsychological sequelae, that derive from craniospinal irradiation dose reduction is not entirely clear [38].

So far, gene-based research has identified two subgroups of medulloblastomas, one associated with mutated genes within the Hedgehog pathway (SHH) and the other associated with altered WNT pathway genes [40, 41]. In 2009, Northcott et al. studied a large cohort of medulloblastomas to determine how many subgroups of the disease exist, how they differ, and the extent of overlap between subgroups [42]. They identified four distinct, nonoverlapping molecular variants: WNT, SHH, group C, and group D. The difference between group C and group D is that although MYC is highly expressed in group C and WNT tumors and MYCN is highly expressed in SHH tumors, neither MYC nor MYCN is highly expressed in group D tumors. Their analysis of overall survival demonstrated a marked reduction in survival for children with Group C medulloblastoma regardless of metastatic stage [42].

Previously, the molecular basis of medulloblastomas emerged from the study of hereditary tumor syndromes. For instance, individuals with Gorlin or Turcot syndrome possess germline mutations in the PTCH1 and APC tumor suppressor genes, respectively, and are predisposed to medulloblastoma, among other cancers [43-45]. Studies of the PTCH1 gene in Gorlin syndrome and sporadic medulloblastomas, as well as knockout studies of its mouse homolog, Ptc, have helped to establish a role for aberrant SHH signaling in 25-35% of medulloblastomas [45].

Similarly, the identification of APC mutations in Turcot syndrome and more frequent mutations of CTNNB1 in sporadic cases have implicated the Wnt signaling cascade in 10–15% of patients with medulloblastomas. Furthermore, patients with Li-Fraumeni syndrome have germline TP53 mutations and can have a broad spectrum of cancer types, including medulloblastoma [44, 46].

New insights into the pathogenesis of these tumors have driven Parsons et al. [37] to sequence 225,752 protein coding exons, adjacent intronic splice donor and acceptor sites, and miRNA genes in 22 pediatric medulloblastomas samples (17 samples extracted directly from primary tumors, 4 samples passaged in nude mice as xenografts, and 1 cell line). A total of
225 somatic mutations were identified in this manner including point mutations, small insertions, duplications or deletions, ranging from 1 to 48bp in length. Two interesting observations were made from their research. First, the average number of non-silent somatic mutations (non-synonymous mis-sense, nonsense, indels, or splice site alterations) per medulloblastoma patient was only 8.3, which is 5 to 10-fold less than the average number of alterations detected in the previously studied solid tumors. Second, the proportion of nonsense mutations was over two fold higher than expected given the mutation spectra observed in this tumor type, and the relative fraction of nonsense, insertion, and duplication alterations was higher in MBs than in any of the adult solid tumors analyzed.

Several genes have been identified as candidate cancer genes (CAN-genes) such as MBPTCH1, MLL2, CTNNB1, TP53, MYC, PTEN, OTX2, SMARCA4, MLL3 in medulloblastomas [37]. However, the pathways most highly enriched for genetic alterations had not previously been implicated in medulloblastomas, involved genes responsible for chromatin remodeling and transcriptional regulation, particularly the histone-lysine Nmethyltransferase MLL2. Up to twenty percent of tumors harbored a mutation in a gene within these pathways or in a related gene member: the histone-lysine-N methyltransferases MLL2 and MLL3; the SWI/SNF-related matrix-associated actin-dependent regulator of chromatin members SMARCA4 and ARID1A; and the histone lysine demethylase KDM6B [37].

**SUMMARY: PERSPECTIVES IN BRAIN TUMORS GENOMICS**

Tremendous advances have been made into the genetic and biological understanding of brain tumors. There has been a significant increase in the rate of discovery of mutated genes in brain cancers due to advances in automated sequencing technology and completion of the human genome sequence [47]. Soon it will be possible and affordable to perform global mutational profiling on every patient. One imminent challenge will be how to analyze and store these data in ways that allows for a meaningful impact in the way we treat patients. Deciphering the roles that the myriad of changes harbored by an individual tumor cell play will be central in developing more rational and targeted diagnostic and therapeutic strategies.

**REFERENCES**


