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## Genetic Instability in Paediatric and Adult Brain Tumours

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### 1. Introduction

#### 1.1 Brain tumours in children and adults

Primary Central Nervous System (CNS) tumours are considered to be those that originate in the CNS and usually remain there. Primary CNS tumours, despite not leading the cancer frequency rates, rank first among cancer types for the average years of life lost (Burnet et al., 2005). By contrast with other malignancies, where research has led to the establishment of more successful treatment options, the diagnosis of a CNS tumour, particularly the more malignant histological types, still has devastating effects on the patients and their relatives, not only due to the dismal prognosis of these tumours with extremely high rates of mortality, but also to the great morbidity that actual treatment options cause (Laughton et al., 2008; Mulhern et al., 2004; Silber et al., 1992).

The estimated annual worldwide age-standardized incidence of malignant primary CNS tumours is 3.5 per 100,000 people, which represents more than 200,000 cases. The rate is slightly higher in males (3.9 per 100,000 people per year) than in females (3.1 per 100,000 people per year) (Ferlay et al., 2008). The frequency of brain tumours is also higher in more developed countries (5.2 per 100,000 people per year) compared to less developed countries (3.0 per 100,000 people per year), probably due to diagnostic advances, as well as access to adequate health care in the developed regions (Ferlay et al., 2008; Wrensch et al., 2005). Similarly, estimated annual global age-standardized mortality of malignant primary CNS tumours is higher in males (3.0 per 100,000 people) than in females (2.2 per 100,000 people), with higher rates also in more developed countries (3.2 per 100,000 people) than in less developed regions (2.3 per 100,000 people) (Ferlay et al., 2008). The median age of diagnosis for all primary CNS tumours is 57 years, however the histology-specific median age ranges from 9 to 70 years ( Central Brain Tumor Registry of the United States [CBTRUS], 2010).

In children, CNS tumours are the second most frequent malignancy after leukaemia and are therefore the most common solid tumours in childhood (Jemal et al., 2009). An estimated 3,750 new cases of childhood primary non-malignant and malignant CNS tumours are expected to be diagnosed in the United States each year. This number reflects an annual incidence rate of 4.5 cases per 100,000 people. As in adults, the rate is higher in males (4.7 cases per 100,000 people) than in females (4.3 cases per 100,000 people) (CBTRUS, 2010). Importantly, malignant brain tumours are the leading cause of cancer-related death in the childhood (Rickert & Paulus, 2001).

Pathologically, CNS tumours are generally classified according to the World Health Organization (WHO) criteria (Louis et al., 2007). There are a wide range of CNS histological entities, classified according to the cell morphology and the degree of malignant behaviour. The WHO classification (Louis et al., 2007) includes a grading scheme that is a reference for predicting the biological behaviour of the tumour. Grade I tumours generally have a low proliferative potential and the possibility of cure after surgical resection, whilst grade IV tumours are histologically malignant, mitotically active and necrotic, and are associated with rapid disease evolution contributing to the high rates of mortality and morbidity among malignant brain tumour patients. The incidence of different histological types of brain tumours varies across specific age groups (Maity et al., 2004); accordingly, the regions of the brain mostly affected in paediatric and adult tumours are also different. In adults and older children, brain tumours are mostly supratentorial (cerebrum), whereas in young children they are more commonly infratentorial (cerebellum) (Gottardo & Gajjar, 2008). This chapter will focus on malignant CNS tumours, more particularly supratentorial high-grade gliomas (WHO grades III and IV) and cerebellar medulloblastomas (grade IV), which are the most common malignant CNS tumours of adults and children, respectively.

Brain tumour aetiology is thought to be multifactorial and is likely to vary by tumour type. There is a likely connection between genetics and environment, meaning that particular genetic susceptibilities lead to increased vulnerability to environmental factors. The only proven exogenous environmental cause of brain tumours, in children or adults, is ionizing radiation, often seen in the setting of previous radiation therapy for the treatment of a former malignancy (Baldwin & Preston-Martin, 2004; Bondy et al., 2008; Ohgaki & Kleihues, 2005; Pettorini et al., 2008; Wrensch et al., 2005). Genetic susceptibility to brain tumours comes from rare syndromes and polymorphisms, specifically in pathways thought to be involved in the process of brain tumour formation. Familial tumour predisposition syndromes are associated with germline mutations, typically in tumour suppressor genes, which confer an increased susceptibility of individuals to tumour formation from childhood until their adult life (Ullrich, 2008). Some of the major syndromes associated with high-grade gliomas or medulloblastomas (with genes affected by germline mutations) are neurofibromatosis type 1 (*NF1*), Li-Fraumeni syndrome (*TP53*) and Turcot syndrome (*APC* and *MLH1/PMS2/MSH2/MSH6*) (complete list in **Table 1**).

## 1.2 High-grade glioma

The majority of CNS tumours in all age groups are gliomas. The estimated annual incidence rate of gliomas in the United States is 6.0 per 100,000 people. Overall, the broad category of gliomas accounts for 36% of all CNS tumours and 81% of malignant lesions. In young adults (20-34 years), gliomas represent 39% of all CNS tumours and 86% of malignant tumours; in adolescents (15-19 years), 45% of all CNS tumours and 81% of malignant; whereas in

Syndrome	Gene	CNS Tumour (e.g.)	Other Clinical Manifestations (e.g.)
Neurofibromatosis Type 1	NF1	Astrocytoma, neurofibroma, optic nerve glioma	Skin café-au-lait spots; axillary freckling; other tumours
Neurofibromatosis Type 2	NF2	Astrocytoma, meningioma	Posterior lens opacities, retinal hamartoma
Tuberous sclerosis	TSC1, TSC2	Giant cell astrocytoma	Other tumours
Li-Fraumeni syndrome	TP53	Astrocytoma, medulloblastoma	Other tumours
Turcot	APC; MLH1, PMS2, MSH2, MSH6	Medulloblastoma; glioblastoma	Skin café-au-lait spots, colorectal polyps
Gorlin	PTCH	Medulloblastoma	Other tumours

Table 1. Familial syndromes and genes involved causing increased risk of gliomas and medulloblastomas. *Adapted from* (Louis et al., 2007).

children less than 15 years the frequency of gliomas is higher (56%), but they only account for 74% of malignant tumours (CBTRUS, 2010). The incidence rates of gliomas by histology varies among age-specific groups; in children and adolescents grade I gliomas are the most common tumours, whereas in older patients grade IV gliomas have the highest incidence (CBTRUS, 2010). The treatment of low-grade gliomas with surgical resection alone allows in most instances the possibility of cure. High-grade gliomas by contrast remain a difficult therapeutic challenge with a poor prognosis. Conventional treatment includes surgery, radiotherapy and chemotherapy, however despite improving survival times and quality of life, current therapeutic regimens are still unable to effect a cure. In malignant histologies, tumour cells infiltrate into the surrounding brain and are generally not completely removed by surgery, which coupled with the fact that these remaining cells are often resistant to radio- and chemotherapy are the main reasons for the therapeutic failure in high-grade gliomas (Imbach, 2006). Similarly in children, surgery plays a major role in the treatment of gliomas, with the extent of tumour resection the most important prognostic factor in this age group. For the more malignant subtypes, focal radiation is used as first line adjuvant therapy, except in infants (Hargrave, 2009; Imbach, 2006). Both in adult and paediatric populations, histological type and grade of the tumour, anatomic location, extent of surgical resection, patient’s age, whether radiotherapy is applied, and some chemotherapy protocols have been consistently considered prognostic factors (Stewart & Cohen, 1998; Wrensch et al., 2005).

The major subtypes of gliomas are astrocytomas, oligodendrogliomas and the mixed lineage, oligoastrocytomas.

Astrocytoma represents a highly heterogeneous histological group of neoplasms. They represent about 75% of all gliomas and can occur in most parts of the brain, and are the most frequent gliomas of childhood (CBTRUS, 2010). While malignant astrocytomas comprise only 2% of all adult tumours, their malignant nature makes them the fourth greatest cancer-related death (Davis et al., 1998). The different histological types of astrocytoma, grade I pilocytic, grade II diffuse, grade III anaplastic and grade IV glioblastoma vary in frequency, age and gender distribution, location within the brain and clinical features. The major malignant subtypes, anaplastic astrocytoma and glioblastoma, account respectively for 8%

and 51% of all gliomas, with glioblastoma representing 80% of malignant tumours (CBTRUS, 2010; Imbach, 2006; Louis et al., 2007; Reifenberger et al., 2006; Weingart et al., 2006). High-grade glioma may arise *de novo*, and are designated primary tumours, or may be considered secondary tumours developing from lower grade lesions. Whereas the great majority of adults with diffuse astrocytoma experience malignant transformation to grade III and finally to grade IV astrocytoma, the long-term risk of malignant transformation in histologically identical neoplasms in children is less than 10% (Broniscer et al., 2007). Nevertheless, the majority (about 95%) of glioblastomas are primary tumours, develop very rapidly in elderly patients (mean 62 years) after a short clinical history and present a poorer prognosis (Louis et al., 2007), whereas secondary glioblastoma mostly develop in younger patients below the age of 45 (Louis et al., 2007). Due to its invasive nature, glioblastoma cannot be completely resected and despite progress in radio- and chemotherapy, less than half of the patients survive more than a year, making glioblastoma the CNS tumour with worse prognosis, for both paediatric and adult patients (Louis et al., 2007; Reifenberger et al., 2006).

Oligodendroglioma account for a small subset of all gliomas (about 8%), being predominantly tumours of adulthood, with a peak incidence between the fourth and fifth decade of life, representing only 1-2% of all CNS tumours in children (CBTRUS, 2010). There are two grades of malignancy for oligodendrogliomas, oligodendroglioma (grade II) and anaplastic oligodendroglioma (grade III), with grading a significant predictor of survival.

Precise data on the incidence of oligoastrocytoma are not available, but reported frequencies vary from 1-20% of all gliomas, with the higher percentage thought to be overestimated due to a consultation bias. These tumours arise preferentially in the cerebral hemispheres and mainly occur in the fifth decade of life (Bromberg & van den Bent, 2009; Louis et al., 2007; Reifenberger et al., 2006; van den Bent et al., 2008). Similar to oligodendrogliomas, these tumours can also be divided in two grades of malignancy.

### 1.3 Medulloblastoma

Medulloblastoma represents a highly malignant, invasive embryonic tumour, and is the most common malignant CNS tumour in children, accounting together with other embryonic tumours for about 1.5% of all primary CNS tumours (CBTRUS, 2010), representing 12-25% of childhood brain tumours and only about 0.5-1% of all brain neoplasms in adults (Imbach, 2006; Sarkar et al., 2005; Taylor, 2006). The peak age incidence is 9 years, with 70% of all medulloblastomas occurring in patients less than 16 years of age. In adulthood, 80% of medulloblastomas arise before the fourth decade of life and rarely occur after the fifth decade. About 65% of patients are male (Louis et al., 2007; Reifenberger et al., 2006; Taylor, 2006). The annual incidence of medulloblastoma has been estimated at 0.5 per 100,000 children less than 15 years (CBTRUS, 2010; Reifenberger et al., 2006). Medulloblastoma presents predominantly neuronal differentiation. It is composed of densely packed small round blue cells with carrot-shaped hyperchromatic nuclei, possibly presenting neuroblastic rosettes which are associated with marked nuclear pleomorphism and high mitotic activity (Huse & Holland, 2010; Imbach, 2006; Louis et al., 2007; Taylor, 2006). The WHO classification of CNS tumours recognizes at least five different histological types of medulloblastoma: classic (70-85% of the cases); desmoplastic/nodular (15% in paediatric medulloblastoma compared to 30-40% in adults); anaplastic (about 10-22% of medulloblastomas); large cell (about 2-4% of cases) and medulloblastoma with extensive



nodularity (about 3%) (Brandes et al., 2009; Imbach, 2006; Louis et al., 2007; Taylor, 2006). There is an heterogeneity among medulloblastoma histologic subtypes which exhibit a highly variable clinical behaviour, with the anaplastic and large cell subtypes being associated with worse prognosis and desmoplastic/nodular medulloblastomas portending a more favourable outcome (Gilbertson & Ellison, 2008; Huse & Holland, 2010; Imbach, 2006). About 30% of the medulloblastoma patients, particularly paediatric tumours, present metastasis via the cerebrospinal fluid pathways at diagnosis, whereas spread outside the CNS is a rare event (Carrie et al., 1994; Frost et al., 1995; Reifenberger et al., 2006). Clinical prognostic factors include tumour size, presence of metastasis, age, and amount of tumour resected (Imbach, 2006). Stratification of medulloblastoma involves distinguishing high-risk and standard-risk patients, with high-risk patients those aged less than 3 years, with incomplete surgical resection of the tumour and/or with disseminated disease (Dubuc et al., 2010; Imbach, 2006; Louis et al., 2007). Significant advances have been made in the treatment of childhood medulloblastoma, with the 5-year survival raised to 60% for high-risk disease and 80% for standard-risk tumours, however the long-term side effects of the treatment modalities applied can be severe. Actual treatment includes maximal safe surgical resection and the use of combined radio- and chemotherapy for children older than 3 years. Most therapeutic approaches for high-risk patients include relatively high doses of craniospinal radiotherapy and aggressive chemotherapeutic regimens (Hargrave, 2009; Imbach, 2006). The treatment of infants with medulloblastoma remains highly problematic as radiation therapy is especially damaging for the developing brain of very young children.

## **2. Genetic instability of malignant brain tumours**

Cancer cells usually harbour mutations in oncogenes and tumour suppressor genes. These may play a role in key cellular processes such as proliferation, apoptosis or angiogenesis. Oncogenes are genes whose deregulated activation through mutation, translocation, amplification or over-expression promotes tumorigenesis. Tumour suppressors, on the other hand, play an inhibitory role, and can be inactivated in cancer through mutation, deletion, methylation or transcriptional repression. Genomic instability present in cancer cells occurs mainly through chromosomal instability (CIN) or microsatellite instability (MSI), together with increased frequencies of molecular alterations in cancer regulatory genes (Negrini et al., 2010; Nigg, 2005). CIN refers to the high rate by which chromosome structure and number (by gains or losses) changes over time in cancer cells compared with normal cells and MSI is characterized by the expansion or contraction of the number of oligonucleotide repeats present in microsatellite sequences (Venkatesan & Loeb, 2005).

### **2.1.1 Patterns of copy number change**

CIN is characterised by an increased frequency of chromosomal alterations, resulting in gains, losses, deletions, insertions, translocations, amplifications, and rearrangements. Nearly all human tumours display the CIN phenotype and consequently aneuploidy. Tumours with the CIN usually harbour mutations in oncogenes and/or tumour suppressor genes, many of which are involved in the regulation of transcription (Nigg, 2005). During the last decade, the use of genome-scale profiling techniques to identify the key genetic alterations underlying different tumour types allowed fundamental findings about the drivers of oncogenesis, providing the rationale for specific targeted therapies in these malignancies. The first studies

using large-scale genome profiling techniques to identify the key genetic alterations of brain tumours were only recently published (Kool et al., 2008; Parsons et al., 2008; The Cancer Genome Atlas Research Network [TCGA], 2008; Thompson et al., 2006). Nevertheless, the number of such studies have been increasing on the past few years, with the first studies in paediatric glioma patients starting to emerge (Barrow et al., 2011; Bax et al., 2010; Paugh et al., 2010; Qu et al., 2010; Schiffman et al., 2010; Zarghooni et al., 2010).

### 2.1.2 High-grade glioma

Comprehensive mapping of the genome of adult glioblastoma has identified common regions of chromosomal instability and gene expression signatures, identifying frequently dysregulated molecular pathways (Bredel et al., 2005; de Tayrac et al., 2009; Gardina et al., 2008; Kotliarov et al., 2006; Maher et al., 2006; Nigro et al., 2005; Parsons et al., 2008; TCGA, 2008). The number of such studies specifically addressing childhood high-grade glioma has until recently been much lower. Nevertheless, several works specifically addressing these paediatric tumours, from ours and others groups, are beginning to emerge, providing increasing evidence that the paediatric high-grade glioma genome has certain key differences from that of histologically similar adult tumours (Barrow et al., 2011; Bax et al., 2010; Paugh et al., 2010; Qu et al., 2010; Rao et al., 2010; Rickert et al., 2001; Schiffman et al., 2010; K.K. Wong et al., 2006; Zarghooni et al., 2010).

These studies have demonstrated that the retinoblastoma (RB), p53 and RTK/PI3K/MAPK pathways are commonly disrupted in adult and paediatric glioblastomas through various genetic mechanisms (TCGA, 2008; Parsons et al., 2008). Nevertheless, our data has demonstrated that paediatric tumours show deregulation of these core pathways by copy number alterations in less than half the frequency of that reported for adult tumours: 25% RTK/PI3K/MAPK, 19% p53 and 22% RB versus 59%, 70% and 66%, for adult glioblastoma (**Figure 1**) (Bax et al., 2010; TCGA, 2008). Even though isolated cases presented clear genomic events linked to activation of the sonic hedgehog (SHH) and Notch pathways activation, there is no evidence of consistently targeted pathways in paediatric high-grade gliomas. Nevertheless, low-frequency amplifications in childhood tumours included genes involved in cell cycle progression (*CCND2*, *CDK4*, *MYC*, and *MYCN*), receptor tyrosine kinases (RTKs) and ligands (*EGFR*, *MET*, *IGF1R*, *PDGFB*, and *NRG1*), members of the PI3K/MAPK pathway (*PIK3C2B*, *PIK3C2G*, *PIK3R5*, *KRAS*, *AKT1*, and *S6K1*), and p53 pathway regulation (*MDM4*), some of them known to be deregulated also in adult glioblastoma (**Figure 2**) (Bax et al., 2010; Paugh et al., 2010). In addition, homozygous deletions of tumour suppressor genes of known importance within the adult glioblastoma core signalling pathways included *CDKN2C*, *PTEN*, *RB1*, *TP53*, and *TP73* (**Figure 1**) (TCGA, 2008; Parsons et al., 2008), albeit at considerably lower frequencies in paediatric *versus* adult tumours. These numerous low-frequency amplifications and deletions identified in paediatric high-grade gliomas, such as *MYC/MYCN*, *CCND2*, *KRAS*, and *CDKN2C*, suggest that paediatric high-grade gliomas may be molecularly more similar to secondary adult glioblastomas (Beroukhi et al., 2007; Maher et al., 2006).

At the gross chromosomal level, paediatric glioblastomas can be distinguished from adult tumours by the more frequent gain of chromosome 1q and loss of 16q, and the relative scarcity of chromosome 7 gains and 10q losses. The most frequent focal amplifications are also different, with *PDGFRA* predominant in paediatric and *EGFR* adult tumours (**Table 2**). Moreover, paediatric cases without *PDGFRA* amplification seem to present overexpression of a specific *PDGFRA*-associated gene signature, which differs from that observed in adult

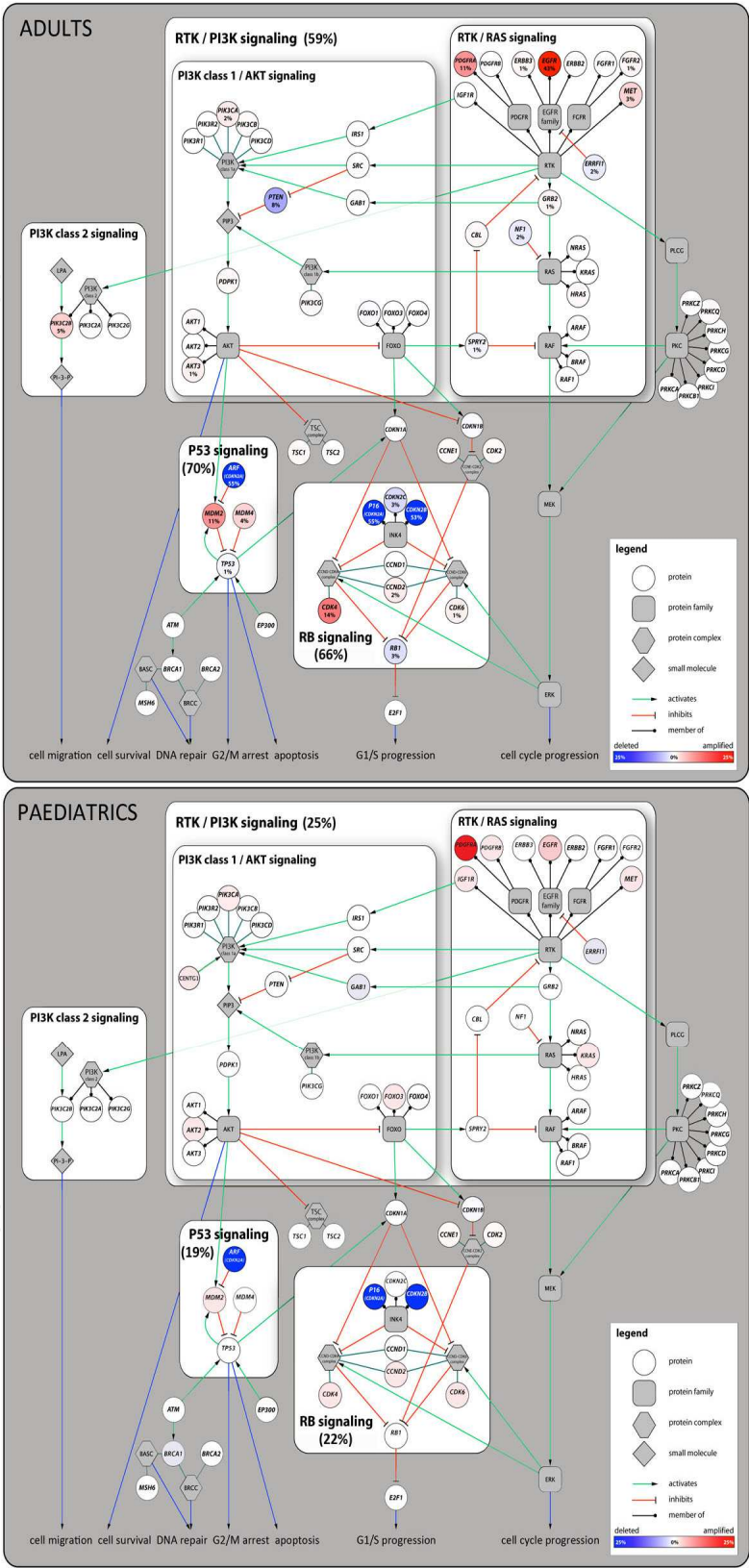


Fig. 1. Copy number alterations in core signalling Pathways in Adult and Paediatric Glioblastoma. RTK/PI3K/MAPK, p53 and RB pathways are more frequently deregulated in adult than in paediatric glioblastomas. Adapted from (Bax et al., 2010; TCGA, 2008).



tumours with the 4q12 amplification (Bax et al., 2010; Martinho et al., 2009; Paugh et al., 2010; Rickert et al., 2001; K.K. Wong et al., 2006). Even if *PDGFRA* amplification, 1q+ and 16q- events are more common in paediatric patients (Qu et al., 2010; Schiffman et al., 2010; Zarghooni et al., 2010), they are also present in a proportion of adult tumours. Similarly there is a small group of paediatric high-grade gliomas containing copy number alterations associated with adult tumours (*EGFR* amplification, 7+, 10q-) (Bax et al., 2010; Paugh et al., 2010). The deletion of *CDKN2A/CDKN2B* is among the most frequent focal events found in paediatric high-grade gliomas, nevertheless it is even more commonly present in adult tumours (**Table 2**) (Bax et al., 2010; TCGA, 2008; Paugh et al., 2010). In adults, secondary glioblastomas show overexpression or amplification of *PDGFRA* but rarely contain *EGFR* aberrations.

Region	Paediatric Glioblastoma (n=46)	Adult Glioblastoma (n=189)	P
Gains			
1q	30%	9%	0.001
7	13%	74%	<0.001
Losses			
1p	9%	2%	0.05
4q	22%	2%	<0.001
9p	17%	33%	<0.05
10q	35%	80%	<0.001
16q	24%	7%	0.003
Focal amplifications			
<i>PDGFRA</i>	16%	11%*	0.2
<i>EGFR</i>	4%	43%*	<0.001
Focal deletions			
<i>CDKN2A</i>	20%	55%*	<0.001

\* n = 206 tumours

Table 2. Summary of copy number changes in Paediatric and Adult Glioblastoma. Adapted from (TCGA, 2008; Paugh et al., 2010).

Recently, missense mutations in *IDH1* were found in a significant number of adult glioblastomas that tend to occur mostly in younger patients with more protracted clinical courses (Parsons et al., 2008). These mutations were found exclusively on the R132 residue in the active site region of the protein (Parsons et al., 2008; Yan et al., 2009). Interestingly, a separate group of gliomas harbour mutations in the *IDH1* homologue *IDH2* at the analogous residue (R172). Further investigations have shown that mutations in *IDH1* and *IDH2* are present in high proportions of grade II and III astrocytic, oligodendroglial and mixed tumours (72 to 100%) along with secondary glioblastomas (up to 85%), but are largely absent in primary glioblastomas (5%) (Hartmann et al., 2009; Ichimura et al., 2009; Parsons et al., 2008; Watanabe et al., 2009; Yan et al., 2009). Additionally, *IDH* mutations are associated with other genomic abnormalities that are typically seen in gliomas, such as *TP53* mutation in low-grade astrocytoma, and 1p/19q deletion in oligodendrogliomas; they are also mutually exclusive with *EGFR* amplification and chromosome 10 loss (Sanson et al., 2009; Watanabe et al., 2009; Yan et al., 2009). These findings suggest that, although *IDH* mutations

probably contribute to the early evolution of low-grade gliomas, remaining in the higher-grade lesions, they seem to have no role in the underlying biology of primary glioblastoma. Importantly, these *IDH1* hotspot mutations are not found in childhood tumours (Balss et al., 2008; Yan et al., 2009), biologically distinguishing paediatric high-grade gliomas from adult secondary glioblastoma. Nevertheless, *IDH1* mutations was recently found in 7 of the 20 high-grade gliomas from older children (14-18 years) and reported to be associated with a favourable prognosis, as observed in adults (Pollack et al., 2010a).

Oligodendrogliomas harbour specific copy number alterations related to response to therapy or prognosis, however a comparison between adult in paediatric populations is difficult, as paediatric oligodendrogliomas are extremely rare neoplasms. Still, up to 80% of adult tumours show combined loss of chromosomes 1p and 19q, associated with increased chemosensitivity to treatment and favourable clinical outcome (Smith et al., 2000, 1999), whereas deletion of these regions are rare and did not seem to anticipate a survival advantage in paediatric high-grade gliomas (Kreiger et al., 2005; Pollack et al., 2003).

Another feature of childhood high-grade gliomas that is almost entirely absent from adult tumours is the occurrence of very few or even no detectable copy number alterations in paediatric tumours (Bax et al., 2010; Paugh et al., 2010). This stable genomic profile is independent of histologic grade or type, and seems to confer an improved survival in high-grade glioma patients, in contrast to those patients with an amplifier genomic profile, who do significantly worse (Bax et al., 2010).

### 2.1.3 Medulloblastoma

Similarly to glial tumours, studies of genomic copy number alterations analysing large cohorts of paediatric and adult medulloblastomas have recently begun to emerge (Kool et al., 2008; Thompson et al., 2006; Korshunov et al., 2010).

The most frequent and consistent genetic event reported in medulloblastoma is the partial or complete loss of the chromosome 17p, often in association with gain of chromosome 17q (resulting in the isochromosome 17q: i(17)q), occurring in approximately 30-50% of the medulloblastomas (Biegel et al., 1997; Bigner et al., 1988; Cogen & McDonald, 1996; Lamont et al., 2004; Nicholson et al., 2000; Steichen-Gersdorf et al., 1997; Capodano et al., 1994). Although the precise mechanism by which this genomic abnormality contributes to tumorigenesis and its prognostic importance remain unclear, the common deletion region of 17p13.2-13.3 includes several confirmed and putative tumour suppressor genes, including *TP53* (Huse & Holland, 2010). Together with the deletion of 17p, *MYC* amplification is a molecular prognostic factor of medulloblastoma (Imbach, 2006). Genomic amplifications of *MYCN* and *MYC* were described as characteristics of a subset of clinically aggressive medulloblastomas that tend to exhibit large cell/anaplastic histological features (Aldosari et al., 2002; Tomlinson et al., 1994).

Recently, Korshunov and colleagues (Korshunov et al., 2010) compared a large series of adult and paediatric subsets of tumours, using array-based comparative genomic hybridization (aCGH) (34 adult and 101 paediatric patients) and validating the results in an independent series (112 adult and 303 childhood patients) by fluorescent *in situ* hybridization (FISH) analysis. Although frequencies of loss of 17p (either isolated or via i(17)q formation) were similar in both populations, isolated gains of 17q were significantly more frequent in children than adult patients, with monosomy of chromosome 17 exclusively found in adults (**Table 3**) (Korshunov et al., 2010). Additionally, amplifications of *MYC*/*MYCN* prevailed in the paediatric cohort, whereas amplification of *CDK6* (at

7q21.3), was frequently present in adult tumours and absent in paediatric medulloblastomas. Of note is that both MYC/MYCN and CDK6 amplifications were associated with poor survival in paediatric and adult populations, respectively. Besides chromosome 17q, alterations on additional chromosome arms were shown to be significantly different between adult and paediatric medulloblastoma. Gains of chromosome 3q, 4 and 19 more frequently found in the adult tumours, while gains of 1q, 2 and 7 and loss of 16q was more abundant in children. The frequency of chromosome 6 deletions was similar across adult and childhood medulloblastoma, however the patterns of aberration were different, with complete loss of the chromosome and absence of concomitant aberrations frequently more present in paediatric medulloblastoma (Korshunov et al., 2010). This may explain the reason why the prognostic value of chromosome 6 deletion, a well established marker for favourable outcome in medulloblastoma (Clifford et al., 2006; Pfister et al., 2009; Thompson et al., 2006), was not found to be statistically significant for adult cases (Korshunov et al., 2010). A summary of the results from the validation cohort is presented on **Table 3**.

Region	Paediatric Medulloblastoma (n=303)	Adult Medulloblastoma (n=112)	P
Gains			
1q	24%	9%	<0.001
2	15%	6%	0.02
6q	11%	3%	*
7	33%	14%	<0.001
17q	17%	2%	**
Losses			
6q	12%	15%	*
17p	4%	4%	**
Focal amplifications			
CDK6	0.3%	8%	<0.001
MYC/MYCN	14%	3%	<0.001
Other Alterations			
i(17)q	39%	32%	**

\* P = 0.02 for total Chromosome 6 aberrations; \*\* P < 0.001 for total Chromosome 17 aberrations

Table 3. Summary of copy number changes in Paediatric and Adult Medulloblastomas (validation set of adult tumours by FISH analysis). *Adapted from* (Korshunov et al., 2010).

2.2 Microsatellite Instability

DNA is continuously exposed to numerous different insults, endogenous and exogenous, that can ultimately result in DNA mutation and alteration of cell behaviour. DNA repair mechanisms are therefore essential for maintaining DNA integrity and preventing tumorigenesis (Li, 2008; Ljungman, 2010). Consequences of the failure of these molecular pathways are well illustrated in colorectal cancer, mainly HNPCC where it is present in about 90% of the tumours. In these cancers, mismatch repair (MMR)-deficient cells adopt a mutator phenotype in which there is a significant increase in cellular mutation rates (Loeb, 1991; Marra & Jiricny, 2005). The most obvious molecular signature of this mutator phenotype is the presence of microsatellite instability (MSI) (Fishel & Kolodner, 1995).

The MMR system is the major pathway responsible for repairing base-base mispairs and short insertion/deletion loops that arise during DNA replication and as intermediates of homologous recombination (Arana & Kunkel, 2010; Kunkel & Bebenek, 2000; Nigg, 2005). Such a mechanism is essential to the cells because the fidelity of replicating DNA polymerases is insufficient to generate an error-free copy of genomic DNA. Single-base substitutions are estimated to arise once in every  $10^4$ - $10^6$  nucleotides incorporated, and MMR reduces the error rate to a range of  $10^{-9}$  to  $10^{-10}$ , which ensures that the human genome can be duplicated without mutations (Kunkel & Bebenek, 2000). Left unrepaired, these structures will give rise to base-substitution and frameshift mutations, respectively (Arana & Kunkel, 2010; Kunkel & Bebenek, 2000; Nigg, 2005). The role of the key factors of the human MMR system, the MutS homologues MSH2, MSH3 and MSH6, and the MutL homologues MLH1 and PMS2, have begun to be elucidated (Jiricny, 2006; Li, 2008; Schofield & Hsieh, 2003). MSH6 competes for binding to MSH2 with MSH3 (Boland et al., 2008), whilst MLH1 can form heterodimers with PMS2 (Li & Modrich, 1995), PMS1 (Raschle et al., 1999) or MLH3 (Lipkin et al., 2000); MLH1/PMS2 is the only complex with an essential role in mismatch correction (Nigg, 2005; Shah et al., 2010).

Microsatellites are short DNA sequence repeats that are scattered throughout the human genome (Lander et al., 2001), and whose copy number varies steadily through evolution (Ellegren, 2004). MSI is the expansion or retraction of the number of repeats within the microsatellites and it is assumed to be generated by slippage of DNA polymerases during copying of repeats, representing a hot spot for mutagenesis (Aaltonen et al., 1994; Cahill et al., 1999; Ionov et al., 1993). The classification of MSI more commonly adopted takes into account the number of markers presenting frameshift alterations. MSI tumours are therefore classified as MSI-H when, comparing to germline DNA, two or more markers present allelic shifts, or in the absence of constitutive DNA, at least three markers are altered. When one or two markers present alterations tumours are classified as MSI-L; when all markers are normal tumours are classified as microsatellite stable (MSS) (Buhard et al., 2006; Umar et al., 2004; Y.F. Wong et al., 2006). In parallel with this classification, an alternative qualitative distinction of MSI, which considers the size of the allelic shifts in the markers, has been proposed (Giunti et al., 2009; Oda et al., 2005). Samples presenting small length changes ( $\leq 6$  bp) are designated Type A MSI whereas those with more extreme variations are defined as Type B MSI.

The presence and frequency of MSI in brain tumours is a controversial and poorly studied issue. Previous studies have evaluated the presence of MSI in brain tumours, particularly in gliomas, while in medulloblastomas MSI status has not been properly addressed. Reports in the literature describe the absence or rare incidence of MSI in adult patients, while in children results have been contradictory, with reported frequencies in paediatric gliomas varying between 0 and 44% (Alonso et al., 2001; Amariglio et al., 1995; Cheng et al., 1999; Dams et al., 1995; Eckert et al., 2007; Izumoto et al., 1997; Kanamori et al., 2000; Leung et al., 1998; Martinez et al., 2005; Sobrido et al., 2000; Vladimirova et al., 2007). Importantly, the methodologies for determining MSI have been highly diverse, making it difficult to draw accurate conclusions (**Table 4**). To clarify the role of MSI in paediatric *versus* adult malignant brain tumours, our group has used a highly sensitive and robust panel of MSI markers and studied series of high-grade glioma and medulloblastoma of adult and paediatric samples for the presence of MSI (Viana-Pereira et al., 2009, 2011). In our study of high-grade



Reference	Age (years)	Number of cases	MSI (%)	Markers	QMVR or comparison with germline DNA
Pollack et al., 2010b	<21	68	3 (4.4%)	Mononucleotide and Polynucleotide*	N/A
Maxwell et al, 2008	N/A	52	8 (15.4%)	Mononucleotide	QMVR
Vladimirova et al., 2007	<18	126	4 (3.2%)	Mononucleotide	-
Eckert et al., 2007	<22	71	0	Mononucleotide	N/A
	<22	553	1 (0.2%)		
Martinez et al., 2005	<18	1	0	Mononucleotide and	Comparison with germline DNA
	>18	108	6 (5.6%)	Polynucleotide	
Alonso et al., 2001	<21	102	16 (15.7%)	Mononucleotide	No
	>21	104	0		
Kanamori et al., 2000	13-19	6	2 (33.3%)	Mononucleotide and Polynucleotide	Comparison with germline DNA
	20-29	8	0		
	>30	66	0		
Sobrido et al., 2000	N/A	56	10 (17.9%)	Polynucleotide	Comparison with germline DNA

\*NCI recommended panel of markers (2 mononucleotide markers: BAT26 and BAT25; and 3 dinucleotide markers: D2S123, D5S346 and D17S250)

N/A - not available

Table 4. Summary of relevant studies reporting MSI analysis in brain tumours after the year 2000.

gliomas, the frequency of MSI was significantly higher in paediatric than adult tumours (Viana-Pereira et al., 2011), reflecting the bulk of the previously published data (Alonso et al., 2001; Cheng et al., 1999; Kanamori et al., 2000; Leung et al., 1998; Martinez et al., 2005). On the other hand, in medulloblastomas, no difference was observed in MSI frequency between adult and paediatric tumours, suggesting that the presence of MSI in these tumours is not age-related (Viana-Pereira et al., 2009). Overall, it seems that there are less molecular differences between adult and paediatric medulloblastomas than those reported in high-grade gliomas, in concordance with our MSI data.

One of the key considerations in the assessment of MSI is in the use of mononucleotides *versus* polynucleotides in the panel of markers used. In our studies we used a pentaplex of quasimonomorphic mononucleotide markers (NR27, NR21, NR24, BAT25 and BAT26), which is currently regarded as the most sensitive panel of markers available, with distinct advantages over the classic National Cancer Institute panel of markers (2 mononucleotide markers: BAT26 and BAT25; and 3 dinucleotide markers: D2S123, D5S346 and D17S250) to the determine MSI in populations of different ethnicities and in different types of human tumours (Buhard et al., 2004; Buhard et al., 2006; Goel et al., 2010; Y.F. Wong et al., 2006). Importantly, the use of quasimonomorphic mononucleotide markers overcomes the need

for using matching germline DNA, required when using dinucleotide polymorphic markers. Despite this, still there is the need for optimization of the quasi-monomorphic variation range (QMVR) for each marker, as the allelic size estimation for these quasimonomorphic markers can be influenced by the use of specific reagents or the sequencing machine (Goel et al., 2010).

Previous studies have established MSI frequencies in gliomas using polynucleotide markers only, with frequencies ranging from 0 to 37% (Amariglio et al., 1995; Dams et al., 1995; Izumoto et al., 1997; Sobrido et al., 2000). Including both mononucleotide and polynucleotides repeat markers did not improve consistency, with contrasting results varying between 0 and 44% in paediatric gliomas cohorts or between 0 and 18% in adult tumours (Cheng et al., 1999; Kanamori et al., 2000; Leung et al., 1998; Martinez et al., 2005; Pollack et al., 2010b). Using mononucleotides only also provided contradictory results of 0 to 27% MSI in paediatric gliomas (Alonso et al., 2001; Eckert et al., 2007; Vladimirova et al., 2007). In addition to the heterogeneity of markers used to assess MSI frequency that likely accounts for the majority of variability in the data, many of the previous studies did not refer the establishment of a QMVR (for quasimonomorphic mononucleotide markers) or a direct comparison between tumour and germline DNA (for other markers).

In contrast to colorectal cancer, which presents mainly Type B MSI, we and others have shown that high-grade gliomas harbour Type A MSI (Giunti et al., 2009; Viana-Pereira et al., 2009, 2011). Moreover, we have observed that both MSI-positive medulloblastoma and high-grade glioma presented small length alterations within the microsatellites and hypothesise that this can also contribute for the high variation frequency of MSI in brain tumours reported in the literature (Alonso et al., 2001; Amariglio et al., 1995; Cheng et al., 1999; Dams et al., 1995; Eckert et al., 2007; Izumoto et al., 1997; Kanamori et al., 2000; Leung et al., 1998; Martinez et al., 2005; Sobrido et al., 2000; Vladimirova et al., 2007).

Importantly, the MSI-positive paediatric high-grade glioma mostly presented a stable genomic profile at the chromosomal level, even if microsatellite and chromosomal instability were not mutually exclusive. As mentioned above, the presence of a proportion of tumours with few or absent copy number alterations distinguishes paediatric high-grade gliomas from their adult counterparts and therefore we hypothesise that MSI might represent an alternative form of genetic instability, at least in a proportion of these paediatric tumours with no gross chromosome number alterations.

Mismatch repair deficiencies have been associated with paediatric brain tumours in a hereditary context. Case reports have described MMR germline mutations combined with NF1-like clinical features in children presenting medulloblastoma or high-grade glioma, described as a “mismatch repair-deficiency (MMR-D) syndrome” (summary in **Table 5**)

(Agostini et al., 2005; De Rosa et al., 2000; Giunti et al., 2009; Hegde et al., 2005; Kruger et al., 2008; Menko et al., 2004; Ostergaard et al., 2005; Poley et al., 2007; Roy et al., 2009; Scott et al., 2007; Toledano et al., 2009; Viana-Pereira et al., submitted; Wagner et al., 2003; Wang et al., 1999). Also in our study there was a MSI-H paediatric high-grade glioma with clinical characteristics of NF1 (multiple *café-au-lait* spots). Even though there was no constitutional DNA available for evaluation of MMR germline mutations, data imply that this patient probably present a *MSH6* germline mutation, harbouring a MMR-D syndrome (de Leeuw et al., 2000).

Due to the widespread presence of microsatellites in DNA, mutations are expected to accumulate in the genome of tumour cells due to MMR deficiency, with some alterations

Family	Malignancy	Age at diagnosis	Café-au-lait spots	Affected gene	Reference
1	AML Medulloblastoma	6 7	Yes	<i>MLH1</i>	Wang et al., 1999
2	Anaplastic oligodendroglioma/ Colorectal cancer Neuroblastoma	14 / 17 18 13	NS NS	<i>PMS2</i>	De Rosa et al., 2000
3	Oligodendroglioma Rectosigmoid carcinoma	10 12	Yes	<i>MSH6</i>	Menko et al., 2004
4	Glioblastoma	8	Yes	<i>MSH6</i>	Hegde et al., 2005
5	Duodenal adenocarcinoma Colonic adenoma Glioblastoma	16 16 17	Yes	<i>PMS2</i>	Agostini et al., 2005
6	Pilocytic astrocytoma Lymphoma Spinal glioblastoma	9 10 2	Yes Yes	<i>MSH6</i>	Ostergaard et al., 2005
7	Glioblastoma Wilms tumour	4 4	Yes	<i>MLH1</i>	Wagner et al., 2003 Poley et al., 2007
8	Lymphoma Anaplastic oligodendroglioma Medulloblastoma	4 6 6	Yes Yes	<i>MSH6?</i>	Poley et al., 2007
9	Medulloblastoma AML Colon carcinomas	7 10 13	Yes	<i>MSH6</i>	Scott et al., 2007
10	Glioblastoma Glioblastoma Colorectal cancer Small bowel cancer Urotel carcinoma Glioblastoma	6 6 15 15 15 9	Yes Yes	<i>PMS2</i>	Kruger et al., 2008
11	Glioblastoma	10	Yes	<i>PMS2</i>	Giunti et al., 2009
12	Glioblastoma Glioblastoma	4 12	NS NS	<i>MLH1</i> <i>NS</i>	Giunti et al., 2009
13	Colorectal cancer Astrocytoma WHOII Anaplastic astrocytoma	14 14 13	Yes Yes	<i>MSH2</i> <i>NS</i>	Toledano et al., 2009
14	Medulloblastoma Duodenal adenocarcinoma	16	Yes	<i>PMS2</i>	Roy et al., 2009
15	Glioblastoma	3	Yes	<i>MLH6?</i>	Viana-Pereira et al., submitted

Table 5. Cases reported in the literature with MMR-D associated with brain tumours, including the likely MMR-D cases found in our studies.

potentially contributing to tumorigenesis (Duval & Hamelin, 2002). Genes thought to harbour mutations in microsatellites due to the MSI phenotype are commonly designated MSI target genes. There are numerous MSI target genes described, however the relevance of several of them in cancer is not clear-cut (Mori et al., 2001; Woerner et al., 2003). In brain tumours, only a small number of the “classical” mutated MSI target genes have been reported: *IGFIIR* (Leung et al., 1998) and *PTEN* (Kanamori et al., 2000), each of them in a single case of MSI high-grade gliomas, and *TGF $\beta$ RII*, reported in 71% of samples (Izumoto et al., 1997), although this result was never confirmed (Kanamori et al., 2000; Leung et al., 1998). We identified four additional alterations, not previously reported in brain tumours, all in genes involved in different DNA repair pathways: mutations in the *MBD4*, *DNAPKcs*, and *MSH6* genes and a polymorphism in *MRE11* (Viana-Pereira et al., 2009, 2011).

In summary, MSI is present in a subset of medulloblastomas and paediatric high-grade gliomas associated with molecular alterations distinctive of this phenotype, suggesting a potentially new genetic pathway correlated with the development of these tumours. As MSI is associated in other tumour types to a differential response to chemotherapy, the presence of MSI even in a small subset of brain tumours may have important translational implications in these extraordinarily treatment refractory malignancies.

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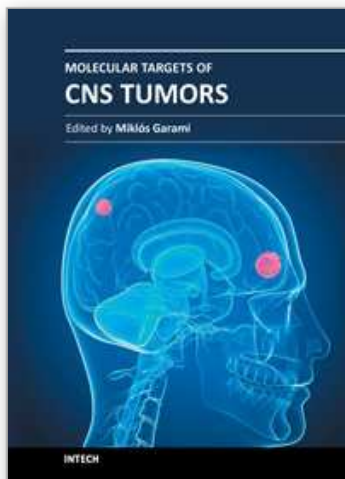
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