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Brain Tumors and the Lynch Syndrome

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1. Introduction

1.1 Clinical features and tumor spectrum

Lynch syndrome (LS) (MIM No. 120435-6), previously known as hereditary nonpolyposis colorectal cancer (HNPCC) (Boland, 2005), is an autosomal dominant disorder caused by germline mutation in one of the DNA mismatch repair (MMR) genes. LS is among the most prevalent cancer syndromes in man and is estimated to account for 1-6% of all colorectal cancers (Lynch & de la Chapelle, 2003).

Before the discovery of DNA MMR gene defects responsible for LS in the 1990s, clinical diagnostic criteria known as the Amsterdam I criteria (Vasen et al., 1991) were used to identify families likely to represent LS. The original criteria were based on colorectal cancer only and were subsequently modified to include extracolonic cancers as well (Amsterdam II criteria, Vasen et al., 1999 (Table 1). Amsterdam II criteria include colorectal cancer, cancer of the endometrium, small bowel, ureter, and renal pelvis as unequivocal manifestations of the syndrome. Later experience incorporating epidemiological, clinical, and molecular information has resulted in the expansion of the list of LS-associated tumors. The revised Bethesda criteria (Umar et al., 2004) include, among others, brain tumors as LS-related tumors (Table 1). Individuals that meet at least one of the Bethesda criteria are considered to have suspected LS, and investigating tumors for microsatellite instability (MSI) is warranted as a pre-screening method prior to germline mutation testing. Currently, the definition of LS is a molecular one and the term LS is restricted to families with an identified pathogenic germline mutation in one of the DNA MMR genes (Boland, 2005).

Carriers of a pathogenic DNA MMR gene mutation have a lifetime risk of 10-53% for developing colorectal carcinoma, 15-44% for developing endometrial carcinoma, and less than 15% for other cancers (Aarnio et al., 1999; Watson & Lynch, 2001; Chen et al., 2006; Senter et al., 2008; Baglietto et al., 2010). The risk of developing cancer depends on the predisposing gene, gender and environmental factors. According to Vasen et al. (2001), the cumulative risk of developing brain tumor by 70 years is 1.2% in MSH2 mutation carriers and lower in MLH1 mutation carriers. Even if the life-time risk of brain tumor, compared to many other tumors, is low in LS families, the risk of brain tumors is unequivocally elevated compared to the general population; the calculated fold increase varies between 4 and 6 (Aarnio et al., 1999; Vasen et al., 1996).

Colorectal carcinomas in LS are often diagnosed at an early age (mean, 45-50 years) and the same applies to many extracolonic tumors, at least when compared to the corresponding sporadic tumors (Vasen, 2005). In published series of LS-associated brain tumors (mainly

representing MLH1 or MSH2 mutation carriers), the average age at diagnosis ranges from 33 to 53 years (Vasen et al., 1996; Aarnio et al., 1999; Vasen et al., 2001; Gylling et al., 2008). LS-associated brain tumors may be of diverse histological types, the most common ones being glioblastoma (Aarnio et al., 1999) and astrocytoma (Vasen et al., 1996).

Amsterdam criteria II

There should be at least three relatives with a Lynch syndrome-associated cancer (colorectal cancer (CRC), cancer of the endometrium, small bowel, ureter or renal pelvis): all of the following criteria should be present:

- 1) one should be a first degree relative of the other two;
- 2) at least two successive generations should be affected;
- 3) at least one should be diagnosed before age 50;
- 4) familial adenomatous polyposis should be excluded in the CRC case (s) if any;
- 5) tumors should be verified by pathological examination

Revised Bethesda criteria

- 1) Colorectal cancer diagnosed in a patient <50 y of age.
- 2) Presence of synchronous, metachronous colorectal, or other Lynch syndrome-related tumors*, regardless of age.
- 3) Colorectal cancer with MSI-H phenotype diagnosed in a patient < 60 y of age.
- 4) Patient with colorectal cancer and a first-degree relative with a Lynch syndrome-related tumor, with one of the cancers diagnosed under age 50 y.
- 5) Patient with colorectal cancer with two or more first-degree or second-degree relatives with a Lynch syndrome-related tumor, regardless of age.

*Lynch syndrome related tumors include colorectal, endometrial, stomach, ovarian, pancreas, ureter, renal pelvis, biliary tract, and brain tumors, sebaceous gland adenomas, keratoacanthomas and carcinoma of the small bowel.

Table 1. Amsterdam II and revised Bethesda criteria

The clinical features of LS variants in which the risk of brain tumor is considerably higher than in classical LS, namely Turcot syndrome (TS) and constitutional mismatch repair deficiency syndrome (CMMR-D), will be described in section “The association of brain tumors with hereditary cancer syndromes” below.

1.2 Genetic basis

Predisposition to LS is caused by heterozygous germline mutations in one of four, possibly five genes with verified or putative DNA mismatch repair function, namely MLH1 (MutL homologue 1), MSH2 (MutS homologue 2), MSH6 (MutS homologue 6), PMS2 (Postmeiotic segregation 2), and possibly MLH3 (MutL homologue 3). The great majority of the presently known 3000 unique mutations and variants in MMR genes affect MLH1 and MSH2, with fewer changes in MSH6, PMS2 and MLH3 (<http://www.insight-group.org>; Peltomaki & Vasen, 2004; Woods et al., 2007). Most MSH2 and MLH1 mutations are truncating (Peltomaki & Vasen, 2004; Woods et al., 2007) and result in unstable mRNA and protein. However, one-third of MMR gene

alterations are of missense type and such changes may occasionally complicate the interpretation of immunohistochemical analyses of tumor tissues by leading to stable but non-functional protein. PMS2 and MSH6 mutations in particular may carry a high risk of brain tumors, but - because of reduced penetrance - mainly when biallelic (CMMR-D) (Wimmer & Etzler, 2008).

The mechanism behind constitutional inactivation of a MMR gene is not always genetic (point mutation or large rearrangement) but may be epigenetic (primary or secondary epimutation; Hitchins & Ward, 2009; Ligtenberg et al., 2009). To our knowledge, brain tumor has not yet been reported as part of the variable spectrum of colorectal and extracolonic cancers observed in constitutional epimutation carriers to date (Suter et al., 2004; Morak et al., 2008; Hitchins & Ward, 2009; Niessen et al., 2009) but there is no reason to suggest why brain tumors would not develop in constitutional epimutation carriers.

1.3 Tumorigenic mechanisms

LS generally complies with Knudson's two-hit mechanism of tumorigenesis (Knudson, 1971) where germline mutation in one copy of a DNA MMR gene (first hit) causes cancer susceptibility but cancer initiation additionally requires the inactivation of the remaining wild-type copy (second hit) in a tumor progenitor cell of a somatic target tissue. Somatic loss of the wild-type allele, as evidenced by loss of heterozygosity (LOH), is the predominant mechanism of the second hit (Ollikainen et al., 2007). As a result of inactivation of both allelic copies, tumor tissues from LS patients typically show the absence of the respective MMR protein by immunohistochemical analysis (and occasionally, other MMR proteins as well in a defined pattern (Hendriks et al., 2006). This has been shown to apply to almost all colorectal carcinomas and extracolonic cancers of the LS spectrum, and brain tumors are no different (Gylling et al., 2008).

Inactivation of a MMR gene is believed to initiate tumorigenesis through the failure of one or several essential functions that the MMR system is known to have, including repair of replication errors and a role in DNA damage signaling (Jiricny, 2006). Impaired repair capacity leads to an elevated rate of mutations in important growth-controlling genes as well as instability at random microsatellite sequences ("mutator phenotype", Perucho, 1996). The demonstration of microsatellite instability (MSI) serves as an important biomarker for LS cancers. A panel of five markers (so called Bethesda panel consisting of BAT25, BAT26, D2S123, D5S346 and D17S250) was recommended for screening purposes (Boland et al., 1998). Size shifts at two or more microsatellite loci indicate high-degree microsatellite instability (MSI-H). The mononucleotide repeats BAT26 and BAT25 are particularly sensitive for MSI-H in both familial and sporadic colorectal cancers, but their performance in extracolonic cancers is less well known. Consequently, as will be described below in section "The role of DNA mismatch repair defects in the pathogenesis of brain tumors", an investigation of different cancers from a nationwide cohort of LS families showed that, despite origin from verified MMR gene mutation carriers, MSI-H frequency in tumors varied between 100 and 0%, where the highest frequencies were for ureter, stomach, and colon and the lowest frequency for brain (Gylling et al., 2008).

2. The association of brain tumors with hereditary cancer syndromes

2.1 Main cancer syndromes in which brain tumors are overrepresented

Several inherited cancer predisposition syndromes are known that are associated with increased risk of brain tumors, besides malignancies of other organs (Table 2). Analysis of

germline and somatic alterations in brain tumors from such syndromes may provide valuable clues to the mechanisms of brain tumor development in general. In most cases, the predisposing gene encodes a tumor suppressor protein and the disease is dominant on pedigree level but recessive on cellular level.

The list includes two syndromes that are associated with germline mutation in DNA MMR genes. Co-occurrence of brain tumor with colorectal tumor in the same individual is known as Turcot syndrome (TS) (Turcot et al., 1959). TS can be dominant or recessive. Dominant TS is due to heterozygous mutations in DNA MMR genes (Chan et al., 1999; Lebrun et al., 2007) or the Adenomatous Polyposis Coli (APC) gene (Foulkes, 1995). Recessive TS is due to biallelic mutation in DNA MMR genes (De Rosa et al., 2000; Miyaki et al., 2001; Hegde et al., 2005) and can also be classified under CMMR-D (but not vice versa: only a minority of CMMR-D cases fulfill the diagnostic criteria of TS). The predominant brain tumor in APC-associated TS is medulloblastoma whereas glioblastoma predominates in TS associated with DNA MMR gene mutations (Hamilton et al., 1995).

To date, some 100 patients have been reported who are homozygotes or compound heterozygotes for DNA MMR gene mutations. The term “constitutional mismatch repair deficiency” (CMMR-D) (Wimmer & Etzler, 2008) or “Lynch III” (Felton et al., 2007) has been proposed for such cases. The clinical picture is severe: the patients are affected by hematological malignancy or brain tumor in childhood and those who survive their first tumor are at risk to develop colorectal cancer or other typical LS-associated malignancy in adolescence or early adulthood (Wimmer & Etzler, 2008). The predominant type of brain tumor that develops in CMMR-D is astrocytoma, primarily glioblastoma (Wimmer & Etzler, 2008). The prevalence of hematological tumors may be higher in patients with biallelic MLH1 or MSH2 mutations whereas patients with MSH6 or PMS2 mutations have a higher risk of brain and LS-associated tumors (Wimmer & Etzler, 2008).

Syndrome	Predisposing gene	Mode of inheritance	Characteristic type of brain tumor
Li-Fraumeni	TP53	AD	Astrocytoma, choroid plexus tumor
Neurofibromatosis, type 1	NF1	AD	Optic pathway glioma
Neurofibromatosis, type 2	NF2	AD	Vestibular schwannoma, meningioma
Von Hippel-Lindau	VHL	AD	Hemangioblastoma
Tuberous sclerosis	TSC1, TSC2	AD	Subependymomal giant cell astrocytoma
Gorlin	PTCH	AD	Medulloblastoma
Turcot	APC	AD	Medulloblastoma
	MSH2, MLH1, MSH6, PMS2	AD or AR	Glioblastoma
Constitutional MMR deficiency	MSH2, MLH1, MSH6, PMS2	AR	Astrocytoma (glioblastoma)

AD, autosomal dominant, AR, autosomal recessive.

Table 2. Inherited cancer predisposition syndromes that are associated with increased risk to brain tumors, in addition to malignancies of various organs.

2.2 Molecular characteristics of “syndromic” brain tumors

As evident from Table 2, inherited syndromes are often associated with particular types of brain tumor (Ullrich, 2008). This is likely to reflect a combination of germline and somatic effects. Locus or allelic heterogeneity may explain some of the increased brain tumor risk in certain families. As mentioned above, among MMR genes, PMS2 mutations in particular (and when biallelic) are associated with increased brain tumor risk (Wimmer & Etzler, 2008). Germline mutation in TP53 predisposes to Li-Fraumeni syndrome, and especially families with TP53 missense mutations within the core DNA binding domain suffer from brain tumors (Birch et al., 1994). Some germline mutations may have tissue-specific effects that are mediated by unique mechanisms. For example, the tetramerization domain of the protein product of the R337H mutation in TP53, which is enriched in Brazil, was found to be less stable than that of wild-type p53 and therefore sensitive to disruption at acidic pH (DiGiammarino et al., 2002). This was proposed as an explanation for the frequent occurrence of adrenocortical carcinoma in association with this mutation.

Even in families segregating an identical germline mutation, tumors at different anatomical sites and at different ages develop, as observed in LS/TS (Peltomaki et al., 2001) or Li-Fraumeni syndrome (Malkin, 2004). This has prompted investigators to search for additional germline genetic variations or modifier genes. In carriers of TP53 mutation and especially those of them who were clinically affected, copy number variation frequencies in the germline were found to be significantly elevated compared to healthy controls (Shlien et al., 2008). Moreover, in choroid plexus tumors, germline hemizygous deletions had progressed into homozygous deletions and germline duplications had enlarged in size. It was suggested that in association with constitutional dysfunction of TP53, germline copy number variations may provide a foundation for the development of more striking chromosomal changes in tumors (Shlien et al., 2008). Inherited MMR deficiency could in theory have analogous effects on other genes by causing subtle genetic instability (Fodde & Smits, 2002), although it is yet to be proven.

Compatible with tumor suppressor function and Knudson’s two-hit hypothesis, the wild-type allele of the predisposing genes of the syndromes listed in Table 2 is regularly inactivated in tumors, as shown for MMR genes in TS (Chan et al., 1999; Lebrun et al., 2007), APC in TS (Hamilton et al., 1995), and TP53 in Li-Fraumeni syndrome (Rieber et al., 2009; Seidinger et al., 2010). In the case of MMR genes, inactivation of both copies in a target tissue typically, but not always, results in MSI and a generalized “mutator” phenotype (Gylling et al., 2008). As will be discussed in greater detail below under “The role of DNA mismatch repair defects in the pathogenesis of brain tumors”, brain tumors may constitute an important exception to the general rule. Apart from the inactivation of the alleles of the predisposing gene, additional somatic changes in tumor tissues may make a difference. In TS patients with (heterozygous) germline mutation in MSH2, TP53 inactivation and chromosomal instability were found to be required for the genesis of glioblastoma but not for colorectal carcinoma, which in turn seemed to require TGFβRII frameshift mutation (Leung et al., 2000).

3. The role of DNA mismatch repair defects in the pathogenesis of brain tumors

3.1 Sporadic brain tumors

With some exceptional single reports (Alonso et al., 2001), MSI is generally rare in brain tumors regardless of histology (Table 3). This is true especially when using microsatellite markers recommended for the analysis of colorectal cancers (like the Bethesda panel, Boland et al., 1998,

or panels based on mononucleotide repeats exclusively). Frequencies of MSI from studies using dinucleotide repeat markers alone or in combination with tri- and tetranucleotide repeat markers vary considerably (see e.g., Gomori et al., 2002 and Wooster et al., 1994 in Table 3).

Tumor type	Markers used to study MSI (type of repeat)	Frequency of MSI	Status of MMR protein expression*	Reference
Pediatric malignant astrocytoma	BAT25, BAT26, MONO-27, NR-21, NR-24 (mono) and Penta C, Penta D (penta)	MSI-low (1 unstable marker): 4/126 (3%)	MSH6+ (other proteins not studied)	Vladimirova et al., 2008
Three sets of tumors: <ul style="list-style-type: none">• Pediatric grade III & IV astrocytoma• Pediatric ganglioglioma• Adult grade III & IV astrocytoma	BAT25, BAT26 (mono)	2 unstable markers: 12/45 (27%) 4/17 (24%) 0/98 (0%)	Not studied	Alonso et al., 2001
Two sets of tumors: <ul style="list-style-type: none">• Pediatric high-grade glioma• Adult high-grade glioma	BAT25, BAT26, CAT25 (mono)	MSI-high ($\geq 2/3$ markers unstable): 0/71 (0%) 1/619 (0.16%)	MSH2+, MSH6+ in all MSH2-, MSH6- in the MSI-high tumor	Eckert et al., 2007
Glioma	DCC, D9S171, D10S541, D13S121, D17S520, D19S412 (di) and AR (tri)	1 unstable marker: 4/7 (57%) 2 unstable markers: 2/7 (29%)	Not studied (no mutation in MLH1 or MSH2)	Gomori et al., 2002
Glial and other brain tumors	vWFa, vWFB, DXS981 (tetra) and AR, DM, c-myc (tri) and D2S123, D16S413, D17S796, D16S301, D16S303, D16S588 (di)	1 unstable marker: 1/54 (1.9%)	Not studied	Wooster et al., 1994

Table 3. DNA mismatch repair defects in sporadic primary brain tumors.

Tumor type	Markers used to study MSI (type of repeat)	Frequency of MSI	Status of MMR protein expression*	Reference
Medulloblastoma	NR27, NR21, NR24, BAT25, BAT26 (mono)	MSI-high (≥ 2 unstable markers): 1/36 (2.7%) MSI-low (1 unstable marker): 3/36 (8.3%)	Among MSI cases, MSH6+ in all (other proteins not studied) and MSH6 promoter methylation in 2	Viana-Pereira et al., 2009
Meningioma (NF2 intact)	BAT25, BAT26, BAT40, MSH6 (mono) and D2S123, D5S346 (di)	No unstable markers in any of 25 tumors	Not studied	Tilborg et al., 2006

*+, expressed, -, not expressed

(Table 3., continued)

There is often no demonstration that MSI results from defective MMR. While immunohistochemical studies occasionally implicate one of the MMR proteins in brain tumors with MSI (Eckert et al., 2007; Szybka et al., 2003), correlation between MSI and MMR protein expression remains poor in many cases (Szybka et al., 2003). Hardly any information is available of the molecular mechanisms that could lead to MMR protein inactivation in brain tumors. As for potential inactivating mechanisms, there is evidence that MSH6 is prone to promoter methylation (Viana-Pereira et al., 2009) and mutation (Yip et al., 2009) in sporadic brain tumors. Taken together, deficient MMR seems to play a less important role in brain tumors compared to e.g., sporadic colorectal cancers, among which 15 – 25% are MMR-deficient in virtually all published series (Peltomaki, 2003). As will be discussed below, this does not exclude the potential importance of MMR protein functions other than mismatch repair in various stages of brain tumor development.

3.2 Lynch syndrome-associated brain tumors

Our recent analysis of tumors arising in different organs from LS mutation carriers showed that, like other tumors, brain tumors complied with Knudson’s two-hit hypothesis by displaying the absence of the MMR protein corresponding to the germline mutation, which suggests inactivation of both copies of the MMR gene in question (Gylling et al., 2008, Fig. 1). Studies published to date report frequencies of 75 – 100% for the immunohistochemical loss of MMR protein(s) in brain tumors from heterozygous carriers of MMR gene mutations (Table 4).

Fig. 1. Decreased MMR protein expression corresponding to germline mutation vs. microsatellite instability using Bethesda markers.

The loss of MMR protein expression may (Leung et al., 2000) or may not (Gylling et al., 2008) lead to MSI (Table 4). Since the detection of MSI by conventional techniques requires the presence of at least one major tumor clone which exhibits microsatellite repeat length deviating from the normal allele size, the apparent absence of MSI in brain tumors may have an alternative explanation based on clonal heterogeneity. Our small pool PCR experiments of brain tumors indeed supported the hypothesis since they detected MSI but it was diluted by multiple minor clones with mutant allele frequency below 30% and the high proportion of clones with normal alleles so that the pattern by conventional PCR was microsatellite-stable. The small pool PCR technique we applied is the same that has been used to detect MSI in constitutional non-neoplastic tissues from biallelic MMR gene mutation carriers in CMMR-D (see next section). Studies suggest that the presence of multiple subclones may be a general characteristic of MSI tumors from LS and sporadic settings (Fujiwara et al., 1998; Barnetson et al., 2000).

Since MSI is generally uncommon in brain tumors (see previous section), its presence may pinpoint MMR gene germline mutation carriers (Giunti et al., 2009). In a series of 34 pediatric gliomas of different grades, Giunti et al. (2009) found two with MSI and both patients subsequently revealed germline mutations in MMR genes (biallelic in one and monoallelic in the other case) compatible with TS. Interestingly, a clear qualitative difference in the MSI pattern was evident when a glioblastoma from a TS patient and a colon cancer from an affected relative were compared. Glioblastoma displayed smaller allelic shifts which may make MSI more difficult to discern and supports the idea that the type of MSI varies in tumors of different histological derivation as previously demonstrated for endometrial vs. colorectal carcinomas representing LS (Kuismanen et al., 2002) and sporadic cases (Duval et al., 2002).

Not much is known about the nature of second “hits” that may mediate MMR protein inactivation in LS-associated brain tumors. In analogy to colon cancers in LS (Ollikainen et al., 2007), LOH appears to be the predominant mechanism (Gylling et al., 2008; Chan et al., 1999) whereas promoter methylation is rare or absent (Gylling et al., 2008).

Characteristics of tumor series	Predisposing gene	Markers used to study MSI (type of repeat)	Frequency of MSI	Expression of protein corresponding to germline mutation	Reference
TS or LS (3 glioblastoma multiforme, 1 mixed glioma)	MSH2 or MLH1	BAT26, BAT40 (mono) and TP53, D18S58, D2S123 (di)	MSI-high (≥ 2 unstable markers): 4/4 (100%)	MSH2- in MSH2 associated and MLH1- in MLH1 associated cases	Leung et al., 2000
LS or TS (7 brain tumors of various histology)	MLH1, MSH2, or MSH6	BAT25, BAT26 (mono) and D5S346, D2S123, D17S250 (di)	No unstable marker in any of 7 tumors*	Germline mutation-associated protein lost in 3/4 (75%)	Gylling et al., 2008
TS or LS (1 anaplastic astrocytoma grade III, 1 glioblastoma)	MSH2 or MLH1	Not studied	Not studied	MSH2- in MSH2 associated and MLH1- in MLH1 associated case	Lebrun et al., 2007
TS (2 glioblastomas)	PMS2 (biallelic) in one and MLH1 (mono-allelic) in another	BAT25, BAT26, NR21, NR22, NR24 (mono)	No. of unstable markers: 3/3 (PMS2-associated), 4/5 (MLH1-associated)	Not studied	Giunti et al., 2009

*By small-pool PCR using D5S346 and D2S123, MSI was present in 4/4 tumors tested.

Table 4. DNA mismatch repair defects in brain tumors from heterozygous carriers of MMR gene mutations, representing Lynch syndrome (LS) or Turcot syndrome (TS).

3.3 Brain tumors in constitutional mismatch repair deficiency syndrome

In individuals with homozygous or compound heterozygous germline mutations in MMR genes (CMMR-D syndrome), both alleles of a given MMR gene are inactive from birth and the corresponding MMR protein is absent not only in tumors but in normal tissue as well (Wimmer & Etzler, 2008). Since normal non-neoplastic tissues lack significant clonality which is a prerequisite for the detection of MSI, it is not surprising that conventional PCR reveals no MSI in normal tissues; however, MSI may be detectable by small-pool PCR (Parsons R et al., 1995). In regard to brain tumors from biallelic MMR gene mutation carriers, immunohistochemical studies usually show the lack of a given MMR protein, whereas MSI (by conventional techniques) is present in only a minority (Bougeard et al., 2003; Agostini et al., 2005; Poley et al., 2007; Wagner et al., 2003; Hegde et al., 2005). These observations emphasize the special nature of brain tumors when compared to other (e.g., colorectal) cancers from biallelic mutation carriers. The findings raise the question whether other functions of the MMR proteins (Jiricny, 2006), such as impaired DNA damage

signaling (Agostini et al., 2005; Bougeard et al., 2003), might be more important than postreplicative mismatch repair in brain tumor development. Resistance to alkylating agents, which develops irrespective of MSI in recurrent gliomas (Yip et al., 2009) may lend further support to this possibility.

An interesting feature of CMMR-D is that almost all patients display signs of neurofibromatosis 1, mainly café-au-lait spots, in the absence of germline NF1 mutations. It was found that the NF1 gene is a mutational target in MMR-deficient cells (Wang et al., 2003), making it possible that neurofibromatosis 1 features result from early somatic mutations targeting NF1.

3.4 Therapy-induced defects in DNA mismatch repair genes

The fact that almost all glioblastomas recur and recurrent lesions are fatal within around a year has prompted comparative molecular studies between primary and recurrent brain tumors. Taking advantage of MSI as an indicator of a tumor clone (or clones), Gomori et al. (2002) found intensive clonal selection which may contribute to the recurrence of gliomas. Yip et al. (2009) observed that certain MSH6 mutations were selected in glioblastomas during temozolomide (alkylating agent) therapy and mediated temozolomide resistance, which may in part explain the poor survival associated with recurrent gliomas. Interestingly, the role of MSH6 in temozolomide response did not depend on MSI.

4. Epigenetic alterations in brain tumors

Distinct methylation profiles may accompany different histological types and subtypes of brain tumors. Studies on promoter CpG methylation of tumor suppressor and other growth-regulatory genes have revealed patterns characteristic of astrocytoma (Yu et al., 2004), various glioma subtypes (Uhlmann et al., 2003), and medulloblastoma (Lindsey et al., 2005). Epigenetic changes may correlate with grade; for example, Uhlmann et al. (2003) found that pilocytic astrocytomas, which are grade I tumors, showed no CpG island hypermethylation of growth-controlling genes as opposed to astrocytomas, oligoastrocytomas, and oligodendrogliomas (grade II – III tumors) which were associated with frequent CpG island methylation.

In analogy to sporadic brain tumors, LS-associated brain tumors that we investigated (Gylling et al., 2008, Fig. 2) may also show patterns of tumor suppressor gene promoter methylation characteristic of tumor type, which might become more distinct if larger series of brain tumors from LS patients were available for molecular studies. Furthermore, comparison of tumor suppressor promoter methylation profiles in brain tumors to those in cancers of other organs from MMR gene mutation carriers suggests the presence of organ-specific epigenetic patterns in carriers of even identical predisposing mutations (Fig. 3).

Among 24 tumor suppressor genes tested, colorectal cancers from LS patients showed the highest number of methylated genes whereas brain tumors had the lowest number (Gylling et al., 2008). Promoter methylation is expected to silence the respective tumor suppressor genes and thereby promote tumor formation. The organ-specific epigenetic patterns we observed may thus contribute to the selective tumor spectrum in LS.

Some epigenetic changes may predict treatment response in brain tumors. For example, the repair enzyme encoded by the 0⁶-methylguanine-DNA methyltransferase (MGMT) gene

removes alkyl groups from guanine and thereby counteracts therapy with alkylating agents. If, however, MGMT is silenced by promoter methylation, chemotherapy-induced lesions remain unrepaired in DNA and trigger apoptosis. Promoter methylation of MGMT, which occurs in approximately half of gliomas, is an independent favorable prognostic sign and confers a significant survival benefit from temozolomide treatment (Hegi et al., 2005). Moreover, recent findings indicate that methylated MGMT alleles are enriched in a subpopulation presumed to comprise glioma-initiating cells, even when the original glioblastoma may have only a minority of methylated alleles (Sciuscio et al., 2011). Of note, besides chemotherapeutic drugs, methylated compounds may also be contained in food, and methylation tolerance due to MGMT inactivation by promoter methylation may thus have broader significance in cancer development. For example, it was proposed that MGMT field defect in colorectal mucosa may be an initiating event in colorectal carcinoma by two alternative mechanisms: first, in concert with KRAS mutation allowing a microsatellite-stable phenotype to become malignant and second, in concert with MMR deficiency facilitating the development of MSI cancers (Svrcek et al., 2010).

	TIMP3	APC	CDKN2A	MLH1	ATM	RARB	CDKN2B	HIC1	CHFR	BRCA1	CASP8	CDKN1B	PTEN	BRCA2	CD44	DAPK1	VHL	ESR1	RASSF1	TP73	FHIT	IGSF4	CDH13	GSTP1
Glioblastoma																								
Glioblastoma multiforme																								
Astrocytoma																								
Ganglioglioma																								
Hemangiomablastoma																								
Meningioma																								
Meningioma																								

Fig. 2. Promoter methylation in 24 tumor suppressor genes studied using methylation-specific MLPA (MS-MLPA) assay in LS brain tumors. Black boxes indicate methylation of the tumor suppressor gene, whereas no methylation is shown as a white box.

Fig. 3. Promoter methylation in Lynch syndrome patients. The height of the bar depicts percentage of tumors with methylation at a given gene promoter.

5. Concluding remarks and future directions

As multi-organ cancer syndromes, LS and its variants TS and CMMR-D provide useful models to study carcinogenesis triggered by a failure in the MMR system. Genetic and epigenetic patterns have been revealed that may help explain the organ-specific cancer susceptibility in LS and more generally, the molecular pathogenesis of cancers of different organs. Brain tumors have drawn attention to MMR gene functions beyond the mere correction of replication errors. While information of the predisposing mutation has efficiently been translated into clinical practice and a significant decrease in mortality as a result of regular surveillance has been reported for LS-associated colorectal cancer (de Jong et al., 2006; Jarvinen et al., 2009), mortality remains high for other tumors that are too rare to be screened for, such as brain tumors (de Jong et al., 2006). Biomarkers that could predict which mutation carriers are at risk for which cancers before the actual tumor develops are eagerly awaited but not yet available. Much progress has been achieved in identifying biomarkers that may predict the behavior, prognosis, and treatment response of existing tumors, including those of the brain. Inherited cancer syndromes will no doubt remain important as shortcuts to the understanding of the molecular pathogenesis of brain and other tumors also in the future. Since many such syndromes are relatively rare, collaboration between basic, epidemiological, and clinical researchers continues to be the key to sufficient numbers of cases and specimens for high-quality research.

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Management of CNS Tumors is a selected review of Central Nervous System (CNS) tumors with particular emphasis on pathological classification and complex treatment algorithms for each common tumor type. Additional detailed information is provided on selected CNS tumor associated disorders.

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