The molecular biology of WHO Grade II gliomas

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The WHO grading scheme for glial neoplasms assigns Grade II to 5 distinct tumors of astrocytic or oligodendroglial lineage: diffuse astrocytoma, oligodendroglioma, oligoastrocytoma, pleomorphic xanthoastrocytoma, and pilomyxoid astrocytoma. Although commonly referred to collectively as among the “low-grade gliomas,” these 5 tumors represent molecularly and clinically unique entities. Each is the subject of active basic research aimed at developing a more complete understanding of its molecular biology, and the pace of such research continues to accelerate. Additionally, because managing and predicting the course of these tumors has historically proven challenging, translational research regarding Grade II gliomas continues in the hopes of identifying novel molecular features that can better inform diagnostic, prognostic, and therapeutic strategies. Unfortunately, the basic and translational literature regarding the molecular biology of WHO Grade II gliomas remains nebulous. The authors’ goal for this review was to present a comprehensive discussion of current knowledge regarding the molecular characteristics of these 5 WHO Grade II tumors on the chromosomal, genomic, and epigenomic levels. Additionally, they discuss the emerging evidence suggesting molecular differences between adult and pediatric Grade II gliomas. Finally, they present an overview of current strategies for using molecular data to classify low-grade gliomas into clinically relevant categories based on tumor biology.

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GRADE II of the WHO grading scheme for glial neoplasms⁹¹ comprises 5 distinct diagnoses for tumors of astrocytic or oligodendroglial lineage: diffuse astrocytoma, oligodendroglioma, oligoastrocytoma, pleomorphic xanthoastrocytoma, and pilomyxoid astrocytoma. The WHO system classifies solely based upon histological appearance, and so aggregation of these tumors into a single grade reflects their individual, perceived positions along various spectrums of histological aggressiveness rather than any fundamental genotypic or phenotypic similarities. In fact, these 5 tumors represent molecularly and clinically unique entities, and, for this reason, collectivization of these tumors (along with WHO Grade I gliomas) under the heading of “low-grade gliomas” is rapidly falling out of favor. Nonetheless, Grade II tumors differ considerably from WHO Grade

I, III, and IV gliomas, and so the 5 Grade II gliomas are often discussed together.

Managing and predicting the course of these tumors has historically proven challenging, so basic and translational research in Grade II gliomas continues in the hopes of identifying novel molecular features that can better inform diagnostic, prognostic, and therapeutic strategies. Notable success has been achieved in the identification of abnormalities on the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q) that have practical implications for clinical management, and this achievement has reinvigorated and rapidly accelerated research into Grade II gliomas.

Despite these successes, the literature regarding the molecular biology of WHO Grade II gliomas remains nebulous. The goal of this review is to present a comprehensive discussion of the current knowledge regarding the molecular characteristics of these tumors on the chromosomal, genomic, and epigenomic levels. We have endeavored to clarify the many points of potential confusion and apparent contradiction that exist within this body of work and to highlight both what is known and what is yet to be

Abbreviations used in this paper: AII = WHO Grade II astrocytoma; EGFR = epidermal growth factor receptor; IDH = isocitrate dehydrogenase; LOH = loss of heterozygosity; OAII = WHO Grade II oligoastrocytoma; OII = WHO Grade II oligodendroglioma; PDGF = platelet-derived growth factor; PDGFR = PDGF receptor; PXA = pleomorphic xanthoastrocytoma (WHO Grade II).

investigated. Additionally, we have attempted to organize the data into a logical and organized framework through which it can be more readily understood. A summary of the chromosomal, genomic, and epigenomic changes associated with low-grade gliomas is presented in Table 1.

We have specifically excluded the WHO Grade II tumor of ependymal origin (ependymoma)⁹¹ from this discussion. Despite technically being a “WHO Grade II glioma,” the biology and clinical characteristics of the ependymomas are considerably different from those of the 5 entities that we discuss in this review. We therefore believe that Grade II ependymomas are better treated within the context of a comprehensive discussion of the molecular biology of ependymoma in general.⁸⁷

Diffuse Astrocytoma

Overview

The synonymous terms “diffuse astrocytoma” and “low-grade, diffuse astrocytoma” (AII) refer to tumors of astrocytic origin with relatively low proliferative activity and without obvious anaplastic features on histological examination.¹⁵³ The category comprises 3 histological variants, including fibrillary astrocytoma, protoplasmic astrocytoma, and gemistocytic astrocytoma (sometimes described as “variants”).^{91,134} Overall, these tumors represent approximately 1.6% of all gliomas and 2.1% of astrocytomas and account for 2,700–4,600 new brain tumor diagnoses per year in the US.¹⁵³ They occur with peak incidence in the young adult population (age 20–34 years), where they represent approximately 10.2% of primary CNS tumors, 30.0% of all gliomas, and 25.2% of all malignant brain tumors.¹⁹ In this age group their survival rates at 1, 5, and 10 years are 91.6%, 58.5%, and 40.7%, respectively.¹⁹ However, these tumors are observed across all age groups and are associated with relatively longer survival times in the pediatric population and with relatively shorter survival times in older adults.¹⁹

In the adult population, most AIIs will ultimately progress to anaplastic astrocytomas and then to “secondary” glioblastomas.^{13,64,91} This tendency suggests that AIIs represent an early stage in the evolution of secondary glioblastoma, and many of the molecular characteristics described in AIIs are likely to be early steps along the path to full-scale malignant transformation of the astrocyte. For this reason it is difficult to describe a set of genomic and epigenomic features that are unique to this grade of glioma, and descriptions of the molecular biology of AIIs should be viewed through this lens.

Many molecular investigations include a small number of AIIs as one part of a larger experimental sample containing various grades of glioma. These studies tend to identify genomic and epigenomic changes that occur with relatively low frequency in AIIs and become more prevalent as gliomas progress to higher grades. Reporting the relative frequency of such changes in AIIs adds little to a focused discussion of AII-specific molecular biology, and interested readers should refer to any of a number of texts on high-grade gliomas that place these findings in the context of the molecular pathogenesis and evolution of glioblastoma.^{8,133} Instead, in this section we summarize

TABLE 1: Summary of chromosomal, genomic, and epigenomic changes associated with low-grade gliomas*

Tumor	Chromosomal			Genomic			Epigenomic		
	Common	Additional		Common	Additional		Common	Additional	
All	polysomy: 7 loss: 17p	gain: 8q, 5p, 9, 19p loss: 6q, 10p, 13q, 19q, 22q, X		loss: <i>TP53</i> mutation: IDH1 (canonical R132H)	mutation: PDGF/PDGFR (?), IDH1 (noncanonical) underexpression: <i>TYRO3</i> , <i>CD9</i> , <i>TIMP3</i> , <i>CSPG2</i> , <i>EGFR</i> , <i>NTF3</i>		promoter methylation: ARF, MGMT	inconsistent data	
OII	t(1;19)(q10;p10) – “1p/19q codeletion”	loss: 4, 6, 11p, 14, 22q		mutation: IDH1 (canonical R132H)	mutation: IDH1 (noncanonical) overexpression: <i>EGFR</i> , <i>PDGF</i> , <i>rPTPβ/γ</i>		promoter methylation: MGMT	inconsistent data	
OAI	inconsistent data	t(1;19)(q10;p10) – “1p/19q codeletion”		heterogeneous	mutation: <i>TP53</i>		inconsistent data	inconsistent data	
PXA	gain: 3, 5 loss: 20, 22	inconsistent data		mutation: <i>BRAF</i> V600E	inconsistent data		inconsistent data	inconsistent data	

* All = WHO Grade II astrocytoma; OAI = WHO Grade II oligoastrocytoma; OII = WHO Grade II oligodendroglioma; PXA = pleomorphic xanthoastrocytoma (WHO Grade II).

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those molecular features that appear common to a large proportion of AII. These molecular features may logically be assumed to represent at least some of the functionally significant, early subcellular changes involved in the process of malignant astrocytic transformation, and understanding these features may be the most clinically relevant approach to interpreting the molecular biology of AII.

Chromosomal Abnormalities

The most common chromosomal abnormalities in AII are trisomies or polysomies of chromosome 7,^{91,134} with gains of 7 or 7q observed in approximately 50% of these tumors.^{158,193} Gains in 8q have also been reported to occur with some consistency in AII,¹¹⁶ and gains of 5p, 9, and 19p have also been inconsistently observed.^{133,134,180} Chromosomal losses in AII have been reported most commonly involving 17p^{116,133,185} and less frequently on 6q,¹⁰⁶ 10p, 13q, 19q, 22q, and the sex chromosomes.^{133,134,177}

Genomic Abnormalities

TP53. The *TP53* gene localizes to 17p13.1, and its protein product (p53) is involved in several cellular processes, including cell cycle regulation, response of cells to DNA damage, cell differentiation, and cell death.¹⁵ Activated p53 induces transcription of p21^{Waf1/Cip1}, which regulates cell cycle progression at G₁ via its activity on cyclin-CDK complexes.^{15,16} The activity of p53 is modulated by MDM4 (MDMX) as well as by MDM2, the latter being modulated¹¹⁸ by p14^{ARF}.

Sixty (60%) to 80% of AII have allelic loss on 17p that includes the *TP53* locus,^{133,187,185} and most AII with the retained locus exhibit *TP53* mutations.^{60,66,132,133} This makes complete absence of wild-type p53 the most common genomic abnormality in AII.^{133,177} The incidence of *TP53* mutations is higher in secondary than in primary glioblastoma^{117,119} but does not increase appreciably between AII and glioblastoma,^{160,178,186,187} lending genome-level support to the hypothesis that AII represent an early stage in the evolution of secondary glioblastoma.^{91,118,153} This hypothesis is further supported by the findings that common *TP53* mutations both in AII¹²⁷ and in secondary glioblastomas¹¹⁷ occur at codons 248 or 273 (while the *TP53* mutations observed in primary glioblastomas are more broadly distributed) and that G:C→A:T mutation in CpG islands are more frequent in secondary than in primary glioblastoma. The latter observation suggests that different mechanisms may lead to the acquisitions of the *TP53* mutations seen in these 2 glioblastoma subtypes.^{117,133}

Isocitrate Dehydrogenase. The enzyme isocitrate dehydrogenase (IDH) catalyzes the oxidative decarboxylation of isocitrate to α-ketoglutarate in the citric acid cycle and uses NADP⁺ as a proton acceptor.³⁴ A total of 5 IDH isozymes have been described, although IDH1 and IDH2 are currently believed to be the most relevant to glioma biology. The IDH1 enzyme localizes to the cytosol and peroxisome,³⁴ while the IDH2 enzyme assumes the more classic, mitochondrial localization (<http://www.ncbi.nlm.nih.gov/gene/3418>).

A genome-wide analysis of glioblastoma identified *IDH1* (2q33)¹¹⁵ (<http://www.ncbi.nlm.nih.gov/gene/3418>) gene mutations in 12% of these tumors,¹²⁵ prompting additional investigations into the potential role of *IDH* mutation in glioma biology. Subsequent studies demonstrated that *IDH* mutations are most common in WHO Grade II and III gliomas, as well as in secondary (but not primary) glioblastomas.^{61,199} Approximately 80% of AII have been shown to harbor *IDH1* gene mutations, and *IDH2* (15q26.1) gene mutations are often present in the residual fraction.¹⁹⁹ This finding makes *IDH* gene mutations the most common and consistent genetic abnormality in AII reported to date. Notably, there does not appear to be a statistical association between *IDH* mutations and *TP53* mutations in AII,⁶ although these data remain inconsistent.^{118,190}

The specific IDH1 mutation observed in low-grade gliomas is almost always (> 90%)³⁹ a point mutation at position 132, where wild-type arginine is replaced by histidine in the mutant form (R132H).⁶ This mutation is commonly referred to as the canonical IDH1 mutation. Other, rare mutations at this position include substitutions of arginine with cysteine (R132C), serine (R132S), leucine (R132 L), glycine (R132G), or valine (R132 V),^{6,199} all of which can be described as noncanonical IDH1 mutations. These mutations are all heterozygous, and no truncation or frame shift mutants have yet been described.²⁰⁶ Position 132 belongs to an evolutionarily conserved region representing the binding site of the isocitrate substrate,⁶ and the R132 mutations result in reduced enzymatic activity toward isocitrate.^{61,199,207} Recent kinetic studies have demonstrated that R132 mutations alter the relative affinity of the IDH1 active site, favoring α-ketoglutarate over isocitrate and resulting in increased production of α-hydroxyglutarate in cells harboring the mutation.¹²⁸ Structural investigations have suggested a mechanistic explanation for this observation related to its effects on subunit dimerization,²⁰⁰ and a “dominant inhibition” model, whereby concurrent underproduction of α-ketoglutarate and overproduction of α-hydroxyglutarate may favor oncogenesis, has been proposed.²⁰⁶ Supplementary hypotheses include contributions to oncogenesis through induction of the HIF-α pathway,²⁰⁷ while others suggest that IDH mutations may not be oncogenic but may instead represent protective mechanisms that interfere with the metabolism of tumor cells.²⁰⁹

IDH2 is the only human protein homolog of IDH1 that uses NADP⁺ as a proton acceptor,¹⁹⁹ and its arginine at position 172 (R172) is exactly analogous to R132 in IDH1. Five point mutations have been identified in IDH2, resulting in replacements of R172 with glycine (R172G), methionine (R172 M), lysine (R172 K), serine (R172S), and tyrosine (R172Y).^{84,104,199} Kinetic and structural studies of IDH2 have not been as extensive as those for IDH1, but the strong similarities between these isozymes and the involved mutations suggest comparable underlying biology.

PDGFR. The platelet-derived growth factor receptor (PDGFR) is a tyrosine kinase receptor that interacts with the RAS pathway (and thus the PI3K/PTEN/AKT/mTOR pathway)¹¹⁸ via the SOS-Grb2 intermediary.^{155,195}

As downstream pathways also modulated by the epidermal growth factor receptor (EGFR), PDGFR-associated pathways have been of considerable interest in glioma research.¹¹⁸ This has the potential to lead to some degree of confusion regarding the relative importance of these pathways in AII versus glioblastoma, and it is therefore important to clarify the current molecular evidence regarding PDGFR pathways in AII.

A number of preclinical and translational studies have reported putative roles for various components of the PDGF/PDGFR proteins in the biology of glioblastoma.^{24,90,118} However, despite being described throughout the glioma genomics literature^{91,118} as being overexpressed in up to 60% of AII, firm evidence for PDGFR overexpression in AII is sparse. Two small studies from the early 1990s,^{41,47} each including only 5 AII in their analyses, reported that PDGFR- α appeared overexpressed in gliomas of all grades, including AII. Attempts to validate this finding have been inconsistent,^{55,175} and ascribing an important, functional role to PDGFR- α in AII on the basis of current evidence appears premature. This distinction is even more important given numerous reports suggesting a role for the overlapping EGFR/RAS/PI3K/PTEN/AKT/mTOR pathway in the biology of primary but not secondary glioblastoma¹¹⁸ and the possible mutual exclusivity between p53 mutations and EGFR overexpression.¹⁸⁷ Moreover, EGFR overexpression is currently considered to be one factor that distinguishes primary from secondary glioblastoma, as it is observed in approximately 40% of the former but is rare in the latter.^{28,88,117,118,187} Given these data, it appears that the tyrosine kinase receptor pathways may be of much greater significance to primary glioblastoma biology than to the biology that defines the AII–secondary glioblastoma spectrum.

Other Genomic Abnormalities. A comprehensive meta-analysis¹⁴³ of studies specifically reporting on gene expression in low-grade gliomas performed through 2006 identified only 11 studies^{37,43,55,56,58,77,89,139,148,174,197} describing specific patterns of gene expression in Grade I and/or Grade II gliomas. The investigators summarized these results, then verified the most commonly reported gene expression patterns using real-time reverse-transcriptase polymerase chain reaction.¹⁴³ With regard to gene expression in AII, the authors reported data from 6 studies^{37,55,56,89,139,148} comparing expression in AII versus normal controls. They found consistent evidence for underexpression of the *TYRO3* gene and for overexpression of the genes *CD9*, *TIMP3*, *CSPG2*, *EGFR*, *PDGFRA*, and *NTF3* as well as a single report of overexpression of *KCNN3*.¹⁴³ Comparison between AII and glioblastoma revealed no instances of specific gene overexpression in AII relative to glioblastoma but found consistent evidence for relative underexpression of *NCAM1*, *FN*, *EGFR*, *VEGF*, *IGFBP2*, *IGFBP3*, and *IGFBP5* as well as an isolated report of underexpression of *MMP16*.¹⁴³

In light of the previous comments regarding *PDGFRA* and *EGFR*, additional clarification regarding some of these genomic findings¹⁴³ is necessary. Review of the source publications in which *PDGFRA* and *EGFR* expression differences were noted^{55,56,89} demonstrates rel-

atively small sample numbers, and 2 of the 3 studies^{55,56} were reported by the same research group. One of these studies⁵⁵ reported more than 2-fold overexpression in *PDGFRA* to be present in only 2 of 10 AII analyzed. Accordingly, we caution against drawing firm conclusions from these data regarding the actual role of *EGFR* and *PDGFRA* in AII, as considerable evidence (described above) suggests that these genomic features are more consistently associated with higher-grade gliomas.

Additional reports involving AII genomics include those that characterize expression and propose potential roles for human herpesvirus-6 variants,²² the *LGII*¹² and *BR-3*¹⁹² gene products, and the *SoxD* and *SoxE* gene families¹⁵⁶ in AII biology and in malignant progression of gliomas. Additional research is necessary before definitive conclusions can be made regarding the putative roles and overall significance of these candidate molecules.

Epigenomic Abnormalities

Epigenomic investigations represent a relatively recent area of research in the molecular biology of AII. The most robust epigenomic data involves the *ARF* gene,^{114,188} which localizes to the *CDKN2A* (*INK4/ARF*) locus on chromosome 9 (9p21).^{114,159} Its gene product, p14^{ARF}, binds to MDM2 and stabilizes both MDM2 and p53.^{73,114,159,165} Accordingly, methylation of the p14^{ARF} promoter results in decreased production of the p14 gene product and relative destabilization of MDM2 and p53. In a single study, *ARF* (p14^{ARF}) promoter hypermethylation has been documented in 26% of AII, which was frequently observed in AII without primary p53 mutations.¹⁸⁸ All AII in this study harboring *ARF* (p14^{ARF}) promoter methylation ultimately progressed to secondary glioblastomas.

Similarly, promoter hypermethylation of the DNA-repair gene *O⁶-methylguanine-DNA methyltransferase* (*MGMT*) has also been observed in 63% of AII.¹⁸⁸ Interestingly, limited data suggest that *MGMT* hypermethylation is associated with p53 mutation but is mutually exclusive to *ARF* (p14^{ARF}) gene hypermethylation.^{177,188} Additional reports suggest epigenomic silencing of the *PCDH- γ -AII* (5q31),¹⁸¹ *PTEN* (10q23.31),¹⁹⁴ and *EMP3* (19q13)⁸³ genes in AII, and further investigations are likely to reveal additional instances of epigenomic abnormalities in these tumors.^{21,202}

Clinical Correlations

Few molecular markers have demonstrated prognostic significance in AII. The evidence is most comprehensive for the putative relationship between p53 status and clinical outcomes, but even here the results remain unclear. Early investigations demonstrated no apparent relationship between p53 expression levels and overall survival.⁴⁸ The literature presents conflicting evidence regarding a potential relationship between abnormalities in p53 and malignant progression, with data arguing both for⁶⁵ and against¹⁸⁶ a potential association. Several studies agree, however, that p53 mutation does appear to be associated with an increased likelihood of tumor recurrence.^{65,127,186} One possible explanation for these nebulous findings may be that the relationship between p53

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status and clinical outcomes varies between subtypes of AII. For instance, some investigators have suggested that much of the overall prognostic impact of p53 status may be related to its disproportionate association with the gemistocytic AII subtype.¹²⁷ Another possible explanation may be that specific p53 mutations are associated with unique prognostic profiles. This is exemplified by the apparent correlation between codon 175 *TP53* mutation and an increased risk of progression and malignant transformation.¹²⁷

Other genomic and epigenomic changes may also have prognostic implications. *IDH1* and *IDH2* gene mutations have been suggested as markers of more favorable survival phenotypes,^{84,104,149} although many of the studies in which this has been demonstrated do not necessarily separate AII from oligodendrogliomas. It therefore remains possible that disproportionate overrepresentation of oligodendroglioma in the experimental samples of these studies influenced the results, and the ultimate generalizability of these potential prognostic biomarkers specifically to AII remains to be determined. Overexpression of EGFR^{88,175} (although uncommon in AII) and PDGFR¹⁷⁵ may be associated with shorter survival times in patients with AII. Additionally, *MGMT* promoter methylation has been associated with response to chemotherapy and thus with improved survival in patients with AII.³⁰

Oligodendroglioma

Overview

The synonymous terms “oligodendroglioma” and “low-grade oligodendroglioma” (OII) refer to tumors of oligodendroglial histology with low proliferative activity and without obvious anaplastic features on microscopic examination.¹⁵³ There are no specific histological variants of OII. Among all grades of glioma (excluding glioblastoma), astrocytic histology is 3 times more common than oligodendroglial histology.^{91,133} Oligodendrogliomas occur with peak incidence in the 3rd to 5th decades,^{91,133} and the 1, 5, and 10-year survival rates for OII in adults are 94.2%, 79.5%, and 63.6%, respectively.¹⁹ OII are less common in pediatric patients,⁹¹ but when they do occur in this age group they are associated with better survival rates than those for OII in adults.¹⁹

OII have recently become the subject of considerable attention in translational neurooncology research because they represent the first primary brain tumor that can be routinely and consistently stratified by molecular features into two clinically distinct subgroups. OII with “deletions” of 1p, with or without deletion of 19q, respond well to chemotherapy and are associated with a relatively longer survival, whereas those in which 1p is intact, with or without 19q, behave more aggressively.⁹¹ This finding supports the longstanding concerns of many neurooncologists that histological subtypes of glioma may not adequately capture all clinically relevant variability among these tumors^{95,96} and serves as important proof of principle for ongoing investigations for molecular subclassification of gliomas.

Chromosomal Abnormalities

The most common chromosomal abnormality in OII, occurring in approximately 50% of these tumors (although some report it in more than 80%),^{11,70,74,81,121,136,138,153,180} is a combined “loss” of the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q).^{91,133,138} These tumors demonstrate “loss” of one entire copy of these chromosomal arms due to an unbalanced t(1;19)(q10;p10) translocation,^{40,67} and this finding is commonly (although technically inaccurately) described as, “1p/19q codeletion.” Conversely, partial deletions of these loci⁹¹ or isolated loss of 1p¹³³ are rare. Of the 2 chromosomal losses, 1p has the greater specificity, as 19q losses have been observed in other histological types and grades of glioma.¹⁶² Notwithstanding, 1p/19q codeletion is not completely specific to OII, as it has also been occasionally reported in astrocytomas, oligoastrocytomas,¹³³ and glioblastomas.⁵⁴ Combined losses of 1p and 19q appear to be mutually exclusive of several other molecular abnormalities commonly associated with gliomas, including 17p LOH and *TP53* mutation.^{94,109,172,179} This suggests that the molecular pathway leading to the 1p/19q codeleted OII may be distinct from those involved in other forms of glioma pathogenesis.¹⁷⁷

The exact molecular mechanisms associated with the development of the unique t(1;19)(q10;p10) translocation in OII are not yet fully understood. Recent evidence suggests that the centromeric regions of chromosomes 1 and 19 show a high degree of sequence homology.¹⁷⁶ This has been hypothesized to result in centromeric colocalization of chromosomes 1 and 19, which might promote centromeric instability and thus favor the translocation.^{67,176} Additional investigations regarding the specifics of this process and the clinical and molecular significance of this finding are ongoing.

Additional chromosomal abnormalities have also been reported in OII, although less frequently than 1p/19q codeletions. These include deletions involving chromosome 4, chromosome 6, the short arm of chromosome 11 (11p), chromosome 14, and the long arm of chromosome 22 (22q)^{70,136} and occasional losses of chromosomes 9 and 10.⁹¹ Array-based comparative genomic hybridization has also suggested submegabase deletions associated with OII, including 300- to 550-kb regions on 11q13 and 13q12.¹⁴⁵ The validity and consistency of these focal deletions remain to be determined.

Genomic Abnormalities

1p/19q Candidate Genes. Despite consistent and convincing evidence for 1p/19q deletions in OII, the specific gene(s) whose loss is associated with the unique clinical phenotype of codeleted OII (see below) remains unclear. Proposed candidate genes on 1p include *Notch2* (1p13-p11),¹⁶ *DIRAS3* (1p31),²⁰³ *CDKN2C* (1p32),⁵⁹ *RAD54* (1p32),¹⁰ *CITED4* (1p34.2),¹⁶⁹ *CAMTA1* (1p36),⁷ *DFFB* (1p36),¹⁰¹ *TP73* (1p36.3),²⁶ and *SHREWI* (1p36.32).¹⁰⁰ Because 19q is completely lost in the OII translocation, mapping studies for identification of candidate gene regions on this chromosome have focused on brain tumors of other histological types with partial deletions of

19q.^{45,108,144,162,164} These studies have suggested a potential role for several genes on the 19q3 region,^{108,144,162,164} but additional investigations have not demonstrated consistent mutations of these genes.⁴⁶ Epigenomic studies (see below) suggest potential roles for *ZNF342* (19q13),⁵² *p190RhoGAP* (19q13.3),¹⁹⁶ *EMP3* (19q13.3),¹⁶⁸ and *PEG3* (19q13.4),^{71,170} but definitive evidence for any of these candidate genes has yet to be demonstrated.^{91,157,177}

Isocitrate Dehydrogenase. As in AIIIs, IDH1 (and/or IDH2) mutations are common in OIIs^{6,84,104,118,199} and have been observed in more than 80% of these tumors.¹⁹⁹ Many of the studies regarding the specific mutations and their functional significance have been conducted on mixed populations of AIIIs and OIIs, and thus the IDH1 R132 and the IDH2 R172 mutations are believed to be the relevant abnormalities in both tumor types. Although the high rate of IDH mutations in both AIIIs and OIIs initially suggested that these mutations were independent of other molecular features that distinguished these tumor types,^{6,84,104,118,199} more recent evidence suggests that there may be a high degree of correlation between IDH mutations and chromosome 1p/19q codeletions.⁸⁴ Many of these investigations are conducted in populations with a mixture of OIIs and AIIIs^{6,84} and do not stratify independently by 1p/19q status and WHO grade, limiting the ability to study the relationship in detail. One investigation where stratification was performed, however, demonstrated 1p/19q codeletions in 85% of tumors with IDH mutations, while no tumors with wild-type IDH were found to be 1p/19q codeleted.¹⁹⁹ The pathophysiological significance of this finding remains to be determined.

Other Abnormalities. *EGFR* amplification has been reported in approximately 50% of OIIs, although this represents older data from small studies of relatively few tumors.¹³⁷ PDGFA and PDGFB, as well as their receptors (PDGFR- α and PDGFR- β) appear to be overexpressed in a large percentage of OIIs,²³ making this finding more common among these tumors than in AIIIs. More recently, overexpression of *rPTP β / γ* has been reported to distinguish OIIs from AIIIs.⁴⁴

The role of the *OLIG1* and *OLIG2* bHLH-family transcription factors in oligodendroglioma identification merits specific mention. Data from murine models suggests that the *OLIG* gene products are essential regulators of ventral neuroectodermal progenitor cell fate and oligodendrocyte development.^{87,93,146,208} This led to initial enthusiasm that identification of these markers may assist in the diagnosis of oligodendroglioma.⁹² This enthusiasm has since been tempered by the demonstration that the *OLIG* transcription factors are overexpressed in most neuroectodermal tumors at both the RNA and protein levels.^{1,5,120,140} Accordingly, the diagnostic role of *OLIG1* and *OLIG2* is currently relegated to that of a molecular marker for general neuroectodermal lineage in brain tumors.^{5,87}

Epigenomic Abnormalities

OIIs demonstrate lower levels of MGMT expression than AIIIs.^{153,161} Some evidence suggests that up to 60%–80% of OIIs may exhibit hypermethylation of the

MGMT promoter^{2,27,107} (more common than in AIIIs) and that this hypermethylation correlates with 1p/19q loss,^{27,57} while others have not observed these effects.^{85,189} Additional genes that have been found to be hypermethylated in some OIIs include *CDKN2A* (9p21), *CDKN2B* (9p21), *ARF* (9p21), *RBI* (13q14), *TP73* (1p36.3), *DAPK1* (9q34.1), *ESR1* (6q25.1), *TIMP3* (22q12.3), *THBS* (15q15), and *GSTP1* (11q13).^{2,136}

Clinical Correlations

Perhaps the most widely reported molecular finding with a clinical correlation is the relationship between the combined loss of 1p and 19q and improvements in survival^{31,74,82,150,163} and response to chemotherapy^{18,51,63,72} and radiotherapy.⁹ Data regarding the prognostic significance of *TP53* mutation status and/or LOH at 17p13 specifically in OIIs is limited, but some evidence suggests that these may be independent, unfavorable predictors of overall and progression-free survival.^{102,182} Gains on the long arm of chromosome 8 (8q) may also be associated with poor outcomes in OIIs, but these data are derived from a relatively small study on a population of oligodendrogliomas of mixed WHO grades.⁷⁹ While other correlations between molecular markers and survival or response-to-therapy phenotypes have been reported,^{136,177} these have almost always been studied primarily in OIIIs, making their generalizability specifically to OIIs unclear.

Oligoastrocytoma

Oligoastrocytomas (OAI), also called “mixed gliomas,”⁹¹ represent a unique WHO class of Grade II glioma that is characterized by tumors exhibiting a mixture of astrocytic and oligodendroglial histological morphology. Molecular evidence suggests that this histological class may comprise an unbalanced mixture of 2 primary tumor genotypes—AII and OII.^{91,94,136} This is supported by the observation that 30%–50% of OAIs exhibit chromosome 1p/19q codeletions^{81,94,121,138} (OII-like), while approximately 30% carry *TP53* gene mutations^{94,109,121,138} (AII-like). Moreover, OAIs with 1p/19q codeletions have been observed to exhibit more prominent oligodendroglioma-like features on microscopic examination, whereas those with *TP53* mutations are more histologically similar to astrocytoma.⁹⁴

One study has proposed that chromosomal data may be useful for subdividing OAIs into 4 subclasses.⁶⁹ This approach may be reasonable if OAI is a genotypically distinct tumor type but may introduce unnecessary complexity if it is nothing more than a mixture of AII and OII genotypes. This proposed scheme has not been further validated, but it underscores the translational relevance of determining the true genotypic nature of OAI. Without such data only broad correlations of genotype with phenotype are possible for this WHO class, such as in recent investigations suggesting that 1p/19q codeletions may be a generally favorable prognostic factor in OAIs.²⁹ While addressing this issue is important, it remains difficult to draw from current data firm conclusions regarding the degree to which OAI biology is novel versus the extent to which the biological observations in OAI can be ex-

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plained simply as a mixture of AII and OII genotypes. One directly related but seldom discussed factor that should be considered when interpreting molecular analyses of OAII is the method of extraction of molecular material from the tissue samples. Experimental protocols that homogenize tissue blocks are likely to extract biological samples for analysis that are heterogeneous mixtures of the molecular constituents of both the oligodendroglioma-like and astrocytoma-like tumor regions, while those that use microdissection of specific regions may be more likely to isolate molecular material that is biased toward one of the two constituent cell types. Studies employing the latter methodology are currently lacking, but such investigations are necessary if comprehensive, comparative molecular analyses of the fundamental similarities and differences between tumors classified as OAII, AII, and OII, as well as careful investigations of the clonal origins of OAII, are to be performed.

A Comment on Pediatric Grade II Infiltrating Gliomas

Clinical evidence shows that WHO Grade II infiltrative astrocytomas in pediatric patients have a lower rate of malignant transformation than those in adults (10% vs 90%).¹⁷ These findings suggest that, despite identical WHO classification, pediatric Grade II infiltrative gliomas may represent a unique disease process that could be expected to harbor a novel genotype. Current evidence regarding this hypothesis is nebulous, and it is difficult to draw definitive conclusions regarding the molecular comparability of adult and pediatric Grade II infiltrative gliomas. Although a complete discussion of the molecular differences between adult and pediatric glioma genomics is outside the scope of this review, a brief overview of the current status of these data is beneficial to draw attention to this persistent ambiguity.

Most investigations of specific molecular differences between pediatric and adult low-grade gliomas have thus far been conducted at the chromosomal level. While 50% or more of adult infiltrating gliomas may have some form of chromosomal abnormality,^{11,70,81,121,136,138,158,180,193} rates for comparable abnormalities in pediatric patients have been reported to be relatively lower.^{14,105,113,122,123,141,183,198} Notwithstanding, chromosomal abnormalities in these pediatric tumors are not rare.¹⁰⁵ For example, rates of 1p and 19q loss in pediatric populations may be similar to¹²⁹ or greater than¹¹² those in adults, although they do not appear to be associated with the same prognostic significance in children.¹²⁹

Definitive conclusions regarding the actual rate of chromosomal abnormalities in pediatric diffuse infiltrating Grade II gliomas, as well as the clinical significance of these findings, are difficult to determine on the basis of current data. Most relevant studies combine (often disproportionately) Grade II gliomas with gliomas of other grades for aggregate analyses of “low-grade gliomas.” Aggregation with either pilocytic astrocytomas, in which chromosomal abnormalities are known to be uncommon, or with anaplastic (Grade III) gliomas, in which prognosis may differ, may significantly bias results.^{14,105,112,113,}

^{122,123,129,141,183,198} When the primary data are presented in a manner that allows independent examination of infiltrating glioma karyotypes,^{14,105,113,183} the rates of chromosomal abnormalities generally appear higher in the Grade II subgroup than the rates reported for the aggregate data set. This suggests that disproportionate inclusion of pilocytic astrocytomas may artifactually dilute the commonly reported rates of chromosomal abnormalities in pediatric infiltrative low-grade gliomas and that these may, in fact, approach those of the adult population. Similarly, conclusions regarding the prognostic implications of 1p/19q status in Grade II gliomas may not be generalizable from the population of patients with predominantly Grade III tumors in which it was studied.¹²⁹ Data interpretation is further complicated by the relatively low absolute number of infiltrating gliomas included in many of these studies.

Genomic profiling studies comparing adult and pediatric gliomas suggest that, in general, transcriptome-level differences may exist between these entities,²⁰⁵ but data on differential rates of expression of specific genes are currently limited. Some evidence suggests that *EGFR* overexpression may be relatively more common in pediatric tumors.¹⁶⁶ Conversely, *OLIG2* expression may be relatively less common.¹²⁴ The clinical significance of these findings remains to be determined.

Pleomorphic Xanthoastrocytoma

Pleomorphic xanthoastrocytoma (PXA) was first described as a unique histopathological entity in 1979⁷⁶ and was characterized in subsequent years as an astrocytic tumor unique in its superficial cortical location, histological variability (pleomorphism), prominent xanthomatous cells, predilection toward occurring in the young, distinct clinical course, and favorable response to surgical resection.^{32,91,131} Literature regarding the molecular biology of PXAs is scarce and incomplete, attributable primarily to the rarity of this lesion. Notwithstanding, a few immunological, cytological, and molecular studies have made significant contributions to the present understanding of PXA as a unique pathological process that is genotypically distinct from other WHO Grade II gliomas.

One distinguishing feature of PXAs, supported by molecular and subcellular findings, is the tendency of these tumors to exhibit a dichotomous astrocytic/neuronal genotype and phenotype. Immunopositivity for glial markers, including glial fibrillary acidic protein (GFAP) and S-100 protein, is consistently present, suggesting a primarily astrocytic phenotype.^{36,62,130} However, neuronal markers, including class-III β -tubulin, synaptophysin, neurofilament proteins, SMI-31, and MAP2 immunopositivity have also been reported in 8%–73% of PXAs, suggesting neuronal differentiation.^{36,62,97,130} Ultrastructural analyses support this dichotomy, demonstrating features consistent with both astrocytic (intermediate filaments, lipid droplets, lysosomes) and neuronal (microtubules, dense core granules) differentiation.^{36,49,53}

PXAs may have diploid or polyploid karyotypes,^{53,183,184} and chromosomal studies have reported gains of chromosomes 3 and 5 and losses of 20 and 22.¹⁵¹ DNA loss on chromosome 9 appears to be the most

common regional chromosomal abnormality in PXA, occurring in ~ 50% of these tumors.¹⁹¹ Other, less common subtelomeric and regional losses involve chromosome 17 (10%), as well as 4qter, 6qter, 8p, 9p, 9qter, 10p, chromosome 13, 17pter, 18qter, 21qter, and chromosome 22.^{38,151,191,201} Subtelomeric duplications have been variably reported at 3pter, 8pter, 12pter, 14qter, 16qter, 19pter, and 20pter,³⁸ and regional/subtelomeric gains have been documented on chromosome X (16%), 2p, 4pter, 5, 7, 9q, 11qter, 12, 15q, 19, and 20.^{38,191,201} Translocations have been described involving chromosome 1,^{86,152} and telomeric breakage and fusion events have been reported for chromosomes 1, 15, 20, and 22.¹⁵²

Many molecular features that are commonly observed in other WHO Grade II gliomas are generally absent in PXAs. *TP53* mutations are uncommon;^{35,75,110,126,204} *EGFR* overexpression is absent;⁵⁰ LOH on chromosome 1, 8p, 9p, 10, 17, 19q, and 22q are only rarely observed;^{75,126} and deletions or epigenomic inactivation involving *CDKN2A* or *CDKN2B* are inconsistent (although potentially functionally significant).^{75,191} Conversely, *BRAF* mutations (particularly at the V600E “hot spot”) are common in PXA,^{25,111,154} a molecular characteristic that they share with pilocytic astrocytomas.^{25,154} PXAs are also unique in their expression of wild-type or truncated CD34,¹³⁵ in their expression of MDM2 without gene amplification,⁹⁸ and in their immunophenotypic heterogeneity.⁹⁹ Together, these findings suggest that PXAs may share more molecular similarities with pilocytic astrocytomas than with other WHO Grade II gliomas, and several authors have suggested that PXAs represent a pathophysiological entity distinct from other tumors that nonetheless share the same WHO grade.^{35,38,75,126,173}

It is also important to note that a small subgroup of PXAs is characterized by more aggressive histological features. These are generally designated as “anaplastic PXA” and assigned to WHO Grade III.⁹¹ The clinical behavior of these lesions is more aggressive and the prognosis is worse for these lesions than for their WHO Grade II counterparts.^{4,167,171} Because of their rarity, relatively little is known regarding the unique molecular biology of anaplastic PXAs; moreover, a detailed discussion of the molecular biology of these Grade III tumors is outside the scope of this review.

Pilomyxoid Astrocytoma

Pilomyxoid astrocytomas are WHO Grade II tumors that are closely related to Grade I pilocytic astrocytomas. They are generally hypothalamic/chiasmatic tumors of the very young (< 1 year old) that may have a more aggressive clinical course than traditional pilocytic astrocytomas.⁹¹ As a rare tumor and a relatively recent addition to the WHO scheme, few molecular investigations of pilomyxoid astrocytomas have been performed to date. The most comprehensive is a comparison of copy number changes between pilomyxoid and pilocytic astrocytomas.⁶⁸ This study suggested that both tumors share similar chromosomal changes but that pilomyxoid astrocytomas have relatively more regional chromosomal loss on 2p, 2q, 3q with additional, occasional differential loss on

7p, 9q, 15q, and 20q.⁶⁸ Infrequent differential gains were also noted on 8q.⁶⁸ Specific genomic differences include a high frequency of underexpression of the *ALDH1L1* gene (89%), a finding shared with phenotypically aggressive pilocytic astrocytomas that may be of phenotypic significance.¹⁴² Mutations of *p53* may be a feature of pilomyxoid astrocytomas, although these data are based on an analysis of only 3 samples and are therefore difficult to generalize.³ A single case of *BCR* gene disruption occurring in a pilomyxoid astrocytoma¹⁰³ and variable activation of the hedgehog pathway in 4 pilomyxoid astrocytomas¹⁴⁷ have also been reported.

Molecular Classification of Low-Grade Gliomas

This review highlights a number of molecular characteristics of low-grade glioma subtypes that may have prognostic and therapeutic relevance. However, because the current WHO system relies solely on histological features for classification,⁹¹ there is currently no formal mechanism by which molecular data can be used to improve the accuracy of glioma classification. Additionally, ambiguous WHO criteria can make classification of some low-grade gliomas challenging and can introduce subjectivity that may limit the reproducibility of glioma classification.⁴² Accordingly, several investigators have suggested that molecular strategies for glioma classification be considered, and numerous efforts have been made toward developing these strategies for low-grade gliomas.

While a comprehensive review of the topic of molecular classification of low-grade gliomas is outside the scope of this review, an overview of the proposed general approaches to such classification is appropriate. Several proof-of-principle studies have demonstrated the ability to use molecular data to stratify low-grade gliomas into classes that overlap with the WHO scheme.^{33,95} From here, a number of specific strategies have been applied to the task of molecular classification of these tumors. Approaches based on the expression of single genes or gene products have been successful at resolving some of the difficulties associated with purely histological differentiation between AII, OII, and OAII,⁴⁴ and strategies employing various combinations of genomic and chromosomal data have demonstrated similar success in this task.^{78,109} Classification techniques based solely on genomic data for a small subset of genes have also been successfully applied to the task of molecular stratification of various categories of low-grade gliomas,⁸⁰ as have schemes that use more comprehensive sets of gene expression profiles.^{20,95,197} Recently, epigenomic profiles involving patterns of CpG island methylation have also been used to define subsets of Grade II gliomas with apparent differences in survival phenotype.⁹³ The actual methods for classification using molecular data vary from simple algorithms based on one or a few markers^{44,80,109} to more complex mathematical models based on aggregate molecular data sets.^{33,78,95}

Issues regarding the practicality of implementation and utilization of molecular classification schemes for low-grade gliomas; the accuracy of putative molecular class discriminators; and the optimal approach for maxi-

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mizing research, diagnostic, and clinical utility of molecular classification strategies are yet to be fully resolved.⁴² Nevertheless, there is considerable optimism in the translational neurooncology community that molecular data will ultimately prove to be a useful adjunct for classification of low-grade gliomas.

Conclusions

Molecular and translational research in WHO Grade II gliomas remains an area of active research through which several practical discoveries have already been made. Future investigations in this arena will include attempts to clarify the relative importance of potentially clinically relevant molecular markers, including p53, 1p and/or 19q deletion, and IDH1 and IDH2, endeavors to expand upon preclinical discoveries of novel potential markers, and efforts to incorporate molecular markers into tumor classification strategies. We remain optimistic that significant progress toward further understanding of the pathophysiology, the clinical behavior, and the optimal management of these tumors will continue to be made in the coming years.

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