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# Concomitant 1p/19q co-deletion and *IDH1/2*, *ATRX*, and *TP53* mutations within a single clone of "dual-genotype" IDH-mutant infiltrating gliomas

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Oligoastrocytoma has largely vanished from the current classification of infiltrating gliomas following recognition that the majority of cases can be definitively classified as oligodendroglioma or astrocytoma by molecular studies [12]. However, exceptional cases have been reported of "dual-genotype oligoastrocytomas" with distinct oligodendroglioma and astrocytoma cell populations [5, 11].

We identified two individuals with morphologically homogenous infiltrating gliomas, harboring concurrent *IDH1/2* mutation (oligodendroglioma/astrocytoma), *ATRX* and *TP53* mutations (astrocytoma), and whole arm loss of 1p/19q (oligodendroglioma), within what we predict to be single tumor clones. Case #1 is a 37-year-old male who underwent resection of a left frontal mass, diagnosed as an anaplastic oligoastrocytoma (WHO grade III) (Fig. 1a). Five years later, a new cystic lesion was found in the previous resection cavity, with histological features in keeping with tumor recurrence (Fig. 1a). Using next-generation sequencing (NGS), both tumors were found to harbor *IDH2* (c.515G>A, p.R172K), *TP53* (c.569C>G, p.P190R; c.1006G>T, p.E336*), and *ATRX* (c.3724_3726delinsGG, p.C1242Gfs*36) mutations (Table 1). Chromosome microarray (CMA) analysis of tumor slides (~ 50–60% tumor content) showed whole arm 1p/19q co-deletion and additional genomic alterations (Suppl. Figure 1 and Tables 1, 2).

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Case #2 is a 46-year-old male who underwent resection of a right frontal infiltrating glioma (Fig. 1b); the tumor was positive for IDH1-R132H by immunohistochemistry (IHC) and had widespread overexpression of p53 and loss of ATRX. IHC findings were verified by NGS, with detected *IDH1* (c.395G>A, p.Arg132His), *ATRX* (c.838delT), and *TP53* (c.388C>T, p.Leu130Phe) mutations (Table 2). CMA analysis of tumor slides (~ 40–50% tumor content) demonstrated whole arm 1p/19q co-deletion present in ~ 50% of the analyzed DNA (Suppl. Figure 1 and Suppl. Table 3).

For both tumors, the variant allele frequency (VAF) of *IDH1/2* and *TP53* mutations was found to be approximately half of *ATRX* (± 10% to account for filtered reads with mapping quality < 20) (Tables 1 and 2). Moreover, 1p/19q co-deletion was present in ~ 50–60% of the analyzed DNA, similar to estimated tumor cellularity; FISH experiments demonstrated presence of the co-deletion within the same area in adjacent ATRX IHC slides (Suppl. Figure 2). These observations suggest the 1p/19q co-deletion and the *IDH1/2*, *TP53*, and *ATRX* mutations to be present within a single tumor clone. While partial and isolated deletions within 19q and to a lesser extent 1p have been observed in IDH-mutant astrocytomas (https://www.cancer.gov/tcga), to our knowledge, a tumor harboring concurrent mutations of *IDH1/2*, *ATRX*, *TP53*, and 1p/19q co-deletion has not been previously reported [4]. The biology and classification of these tumors remains uncertain. The absence of a *TERT* promoter mutation is unusual in an oligodendroglioma, and suggests that the 1p/19q co-deletion may have occurred by chance in tumors with an initial astrocytoma genotype (*IDH1/2*, *ATRX*, and *TP53* mutations). In addition to the *ATRX* and *TP53* mutations, the relatively more complex microarray copy-number profiles (Suppl. Figure 1) would be more in keeping with astrocytoma, although complex oligodendroglioma copy-number profiles have also been reported [3]. Both cases also lack *CIC* and *FUBP1* mutations, although these alterations are identified in only about half of oligodendrogliomas [2]. An alternative, though less likely explanation to the origin of these tumors is that in which *IDH1/2* mutations and 1p/19q co-deletion were the initiating events, followed by *TP53* and *ATRX* mutations. This hypothesis is thought-provoking given that *IDH2* mutations are far more frequent in oligondedrogliomas [1]. However, co-occurrence of 1p/19q co-deletion and *ATRX* mutation is unusual [7]. The observation that the frequencies of 1p/19q co-deletion and *IDH1/2*, *ATRX*, and *TP53* mutations paralleled the estimated tumor cellularity in the specimens analyzed made us additionally consider the possibility that these gliomas could represent the concomitant (rather than sequential) acquisition of 1p/19q co-deletion and *ATRX/TP53* mutations, possibly from an early progenitor neuroglial precursor cell pool in a background of increased risk for *IDH1*/*IDH2* mutant glioma development [6]. Lastly, we considered the possibility of two distinct oligodendroglioma/astrocytoma subclones, as has been previously reported [11]. Nonetheless, the VAF ratios and lack of *TERT*-promoter mutation argue against this. Overall, we favor that the presence of *TP53* and *ATRX* mutations will lead to biology and behavior more in keeping with an astrocytoma.

These “dual-genotype” infiltrating gliomas pose a diagnostic dilemma as they do not fit neatly within the current understanding of glioma genetics and classification. Based on WHO 2016 criteria, the tumors reported here would be consistent with the diagnosis of oligodendroglioma, IDH-mutant and 1p/19q co-deleted [9]. However, a common diagnostic

approach, which utilizes immunohistochemistry for IDH1-R132H, ATRX, and p53, would lead to classification of such cases as IDH-mutant astrocytomas [8]. The cIMPACT-NOW update 2 allows for tumors positive for IDH-R132H with loss of ATRX and p53 overexpression (as in Case #2) to be diagnosed as IDH-mutant astrocytomas without 1p/19q co-deletion testing [8]. These results suggest that expansion of recommendations for 1p/19q co-deletion testing may be warranted. However, it remains uncertain which alterations will dictate the tumor phenotype and prognosis, the 1p/19q co-deletion or *ATRX*/*TP53* mutations. As such, these tumors do not fit neatly within the diagnosis of oligodendroglioma. Thus, we suggest classification of such tumors as oligoastrocytoma, IDH-mutant and 1p/19q-codeleted, not elsewhere classified (NEC) or, alternatively, as diffuse glioma, IDH-mutant and 1p/19q-codeleted, NEC. In keeping with the cIMPACT-NOW recommendations, this diagnosis conveys the unusual molecular features and uncertainty with respect to tumor classification [10]. As molecular testing is more widely implemented in the characterization of infiltrating gliomas, it is clear that there are unusual tumors which run counter to our understanding of glioma biology. Larger case series and single-cell sequencing analyses of tumor heterogeneity are needed to clearly define the prognostic implications of these dual-genotype gliomas.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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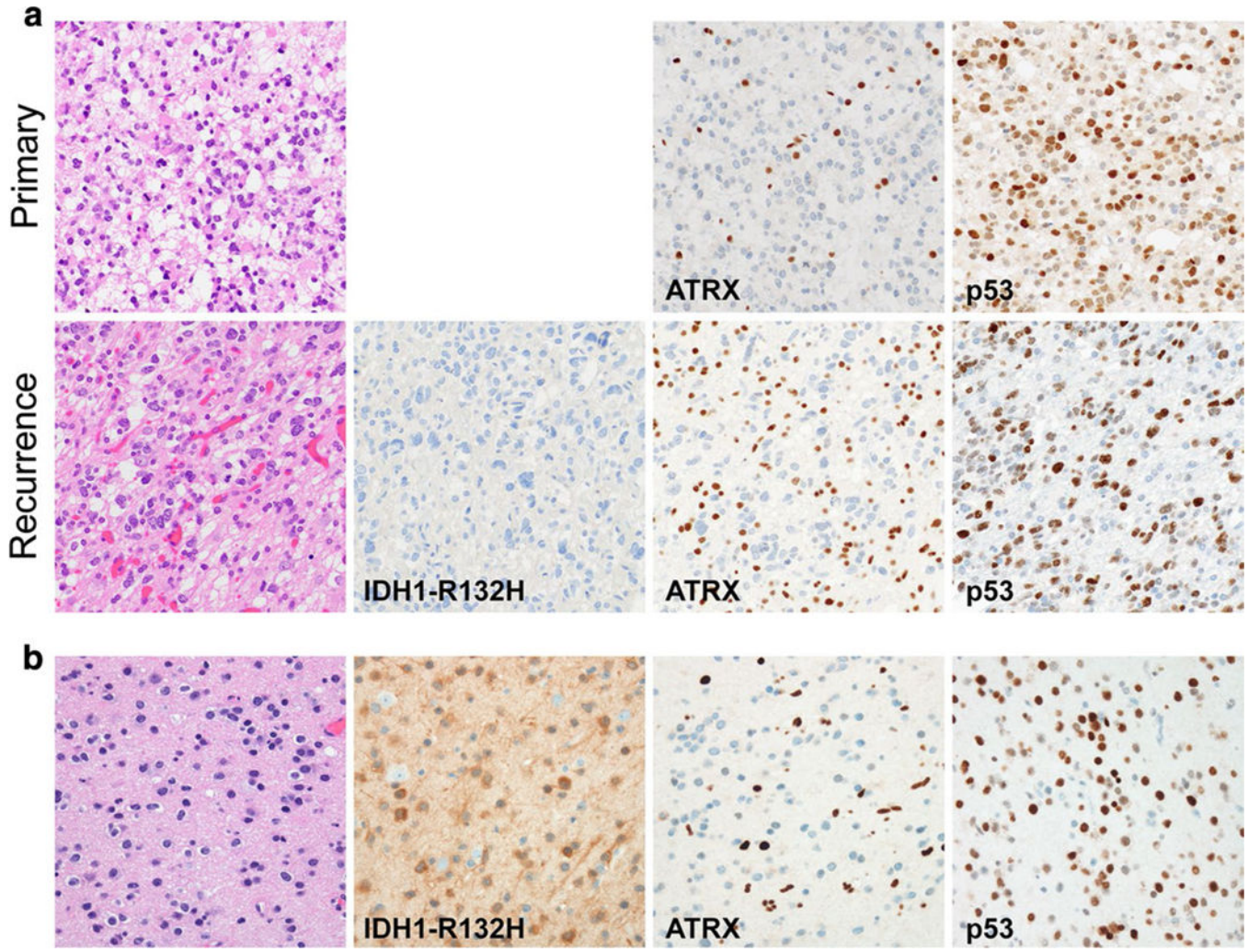


**Fig. 1.**

Histological features of dual-genotype gliomas in this study. **a** Primary moderately cellular infiltrating glioma from Case #1. At tumor recurrence, cells showed greater degrees of atypia and nuclear pleomorphism. Both primary and recurrent tumors were mitotically active without microvascular proliferation or necrosis. IHC was negative for IDH1-R132H, with ATRX loss, and overexpression of p53. **b** Case #2 demonstrated a low to moderately cellular infiltrating glioma with low mitotic activity. By IHC, the tumor was positive for IDH1-R132H, with loss of ATRX expression, and overexpression of p53

**Table 1**

VAFs detected in Case #1′s gliomas using a NGS panel

| Gene | Transcript | Exon | Genomic | cDNA | Variant classification | Primary tumor variant frequency | Recurrence tumor variant frequency |
|---|---|---|---|---|---|---|---|
| *ATRX* | NM_000489.3 | Ex9 | chrX:g.76937020TG>T | c.3727delC | Pathogenic | 0.82 | 0.73 |
| *IDH2* | NM_002168.3 | Ex4 | chr15:g.90631838C>T | c.515G>A | Pathogenic | 0.44 | 0.33 |
| *TP53* | NM_000546.5 | Ex10 | chr17:g.7574021C>A | c.1006G>T | Pathogenic | 0.45 | 0.41 |
| *TP53* | NM_000546.5 | Ex6 | chr17:g.7578280G>C | c.569C>G | Pathogenic | 0.47 | 0.33 |

Notice the doubling of the *ATRX* VAF for this male patient compared to *IDH2* and *TP53* frequencies, present in autosomes

**Table 2**

VAFs detected in Case #2′s glioma using a NGS panel

| Gene | Transcript | Exon | Genomic | cDNA | Variant classification | Variant frequency |
|---|---|---|---|---|---|---|
| *ATRX* | NM_000489.3 | Ex9 | chrX:g.76939909CA>C | c.838delT | Pathogenic | 0.66 |
| *IDH1* | NM_005896.3 | Ex4 | chr2:g.209113112C>T | c.395G>A | Pathogenic | 0.32 |
| *TP53* | NM_000546.5 | Ex5 | chr17:g.7578542G>A | c.388C>T | Pathogenic | 0.77 |

Notice the doubling of the *ATRX* VAF for this male patient compared to *IDH*1, present in an autosome. *TP53* presented with loss-of-heterozygosity (LOH), which is in agreement with the observed mutation frequency being approximately double of *IDH1*