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CORRESPONDENCE

CDKN2A/B mutations and allele-specific alterations stratify survival outcomes in IDH-mutant astrocytomas

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IDH-mutant astrocytomas (IDHA) are initially slow-growing tumors that almost inevitably progress [4]. Homozygous deletion (HOMDEL) of *CDKN2A* and/or *CDKN2B* (*CDKN2A/B*), now a WHO grade 4 defining criterion for IDHA, is associated with rapid progression and poor overall survival (OS) [1, 9]. We examined the prognostic significance of additional *CDKN2A/B* inactivating events, including nonsynonymous mutations and allele-specific copy number alterations (ASCNA) by analyzing 347 prospectively tumor-matched normal sequenced IDHA (347 patients, supplemental table 1) using FACETS (Fraction and Allele-Specific Copy Number Estimates from Tumor Sequencing), a SNP-based algorithm to assess ASCNA across genomic targets [8], with validation using The Cancer Genome Atlas (TCGA, 188 tumors/patients, supplemental methods).

CDKN2A/B alterations were found in up to 15% of IDHA (Fig. 1a, b): 12% exhibited *CDKN2A/B* loss (n = 42/347) and were associated with higher histologic grade (supplemental table 2). *CDKN2A/B* loss, *PDGFRA* gain, and *CDK4* gain associated with shorter OS by multivariable Cox proportional hazards modelling (supplemental Fig. 1e). Nonsynonymous mutations in *CDKN2A* were uncommon (n = 9, 2.6%), but were mostly classified as oncogenic or likely oncogenic by OncoKB™ (n = 6, Fig. 1b, supplemental table 3) [2]. *CDKN2A*-mutant tumors were higher grade and had shortened OS (median OS: 1.6 years, 95% CI: 0.8 years–not reached [NR]) versus non-mutant tumors (median OS: 12.6 years, 95% CI: 11.4 years–NR, $P < 0.001$, Fig. 1c), approximating the OS of tumors with *CDKN2A/B* copy loss (median survival: 3.0 years, CI: 1.4 years–NR) even after excluding hypermutant tumors [10].

FACETS detected hemizygous deletion (HEMIDEL) in 23% of IDHA (n = 81/347), HOMDEL in 6% (n = 21), and copy-neutral loss of heterozygosity (CNLOH) in 3% (n = 11), mostly in high histologic grade tumors (supplemental table 4). The remaining 67% (n = 234) were neutral (supplemental Fig. 2a). Of 305 copy neutral tumors, FACETS detected ASCNA in 75 (25%) demonstrating shorter OS (median 7.0 years, 95% CI: 5.9 years–NR) vs. FACETS neutral (15.4 years, 95% CI: 11.8 years–NR, $P = 0.0014$, Fig. 1d). HEMIDEL IDHA had shorter OS than neutral (median survival: 6.9 years (95% CI: 4.5 years–NR) vs. 15.4 years (95% CI: 11.8 years–NR, $P < 0.001$), but longer OS than HOMDEL/mutant cases (median survival: 2.6 years, 95% CI: 1.3 years–NR, $P = 0.018$, Fig. 1e). CNLOH of *CDKN2A/B* portended poor prognosis (median survival: 2.3 years, 95% CI: 1.6 years–NR, $P < 0.001$, supplemental Fig. 2b). We verified intermediate OS of *CDKN2A/B* HEMIDEL between *CDKN2A/B* HOMDEL/mutant and neutral tumors (Fig. 1f) in the TCGA cohort (supplemental methods). Gains of *CDK4* and/or *CCND2* worsened OS in *CDKN2A/B* HEMIDEL tumors (median

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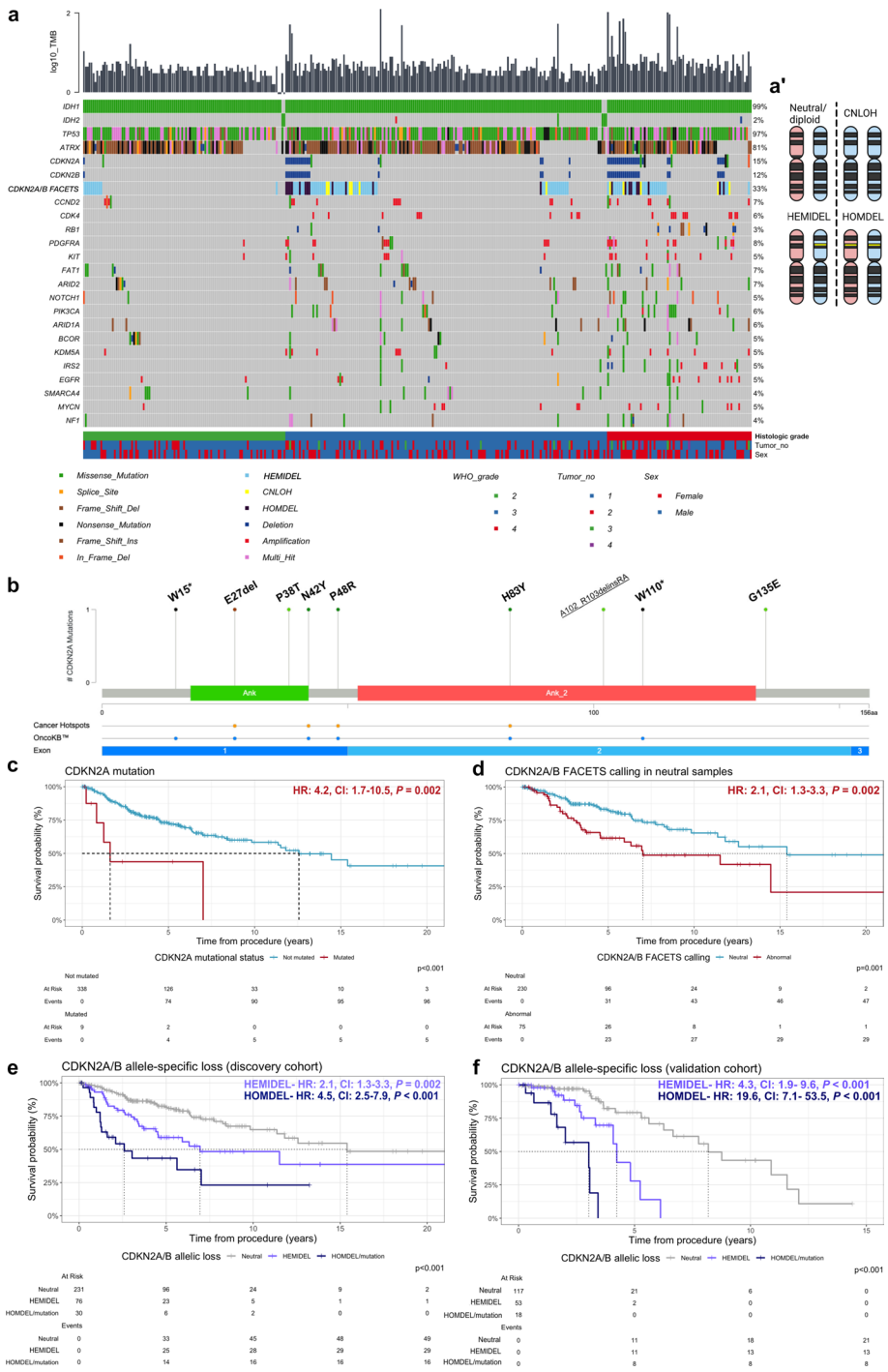

Fig. 1 **a** Oncoplot depicting frequently altered genes and $\log_{10}$ tumor mutational burden (TMB) in 347 IDHA. **a'** CDKN2A/B allele-specific copy number states at 9p21.3. Yellow band = CDKN2A/B deletion, red and blue shades discern parental alleles. **b** Lollipop plots display variants in copy neutral CDKN2A/B (underlined: hypermutant). **c** Nonsynonymous CDKN2A mutations shorten OS. **d** ASCNA in CDKN2A/B copy neutral samples conferred worse OS than FACETS neutral. **e** CDKN2A/B HEMIDEL (n = 76) confers intermediate OS between patients with CDKN2A/B HOMDEL/mutation and CDKN2A/B neutral/without mutation. **f** TCGA validation cohort; HR—hazard ratios, CI—confidence intervals, P values within graphs refer to univariable Cox-proportional hazards regression models, log-rank test

survival: 3.2 years (95% CI: 1.4 years–NR) versus 11.5 years (95% CI: 4.5 years-NR, $P = 0.011$, supplemental Fig. 2c, d).

Matched tumor-normal NGS with FACETS analysis detects a range of prognostically relevant alterations in *CDKN2A/B* and other genes. FACETS showed good concordance with SNP-microarray in a subset of cases (supplemental Fig. 3). Kocakavuk et al. recently described shortened OS across multiple cohorts of IDH-mutant, 1p/19q intact gliomas with *CDKN2A* HEMIDEL using copy number profiles from NGS/methylation data [3]. These findings emphasize the clinical relevance of detection of *CDKN2A/B* HEMIDEL in IDHA. [6, 7]. As a molecularly-targeted therapeutic has shown promise in IDH-mutant grade 2 gliomas [5], extending the utility of NGS with bioinformatic tools like FACETS may help to both improve patient management and guide optimal treatment in the future.

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Data availability The datasets analyzed in the current study are available from the corresponding author on reasonable request.

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