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Even heterozygous loss of CDKN2A/B greatly accelerates recurrence in aggressive meningioma

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A hallmark of aggressive meningiomas is their genomic instability [2, 3]. In fact, the World Health Organization (WHO) recently added homozygous loss of cyclin-dependent kinase inhibitor 2A and/or B (*CDKN2A*, *CDKN2B*)—two tumor suppressor genes adjacent to one another on chromosome 9p21—to their grade 3 (aggressive) meningioma classification [6]. Although not required for grade 3 designation, homozygous loss of either gene is associated with high mitotic count and shorter recurrence-free survival. It is unclear, however, how practical this criterion is for prognosis. First, *CDKN2A/B* deletions seem to be rare [9]. Second, detecting *CDKN2A/B* loss can be difficult, as immunohistochemistry for the protein product may not be reliable [5]. Third, many of these deletions occur in tumors

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already classifiable as grade 3, most of which are recurrences, meaning that they have declared themselves to be aggressive by their behavior even before pathological analysis. To clarify the prognostic value of *CDKN2A/B* loss, we therefore used integrated molecular classification, which predicts outcome much more reliably than WHO grade [1, 4, 7, 8].

We examined 776 tumors from four institutions in total [1, 4, 7], grading them using the 2016 WHO guidelines. We then used methylation (Illumina Infinium MethylationEPIC (850 k) BeadChip) and RNA profiling to classify the tumors as Meningioma Group (MenG) A (benign, merlin-intact), B (benign, merlin-deficient), or C (aggressive) [1, 4, 8]; we determined *CDKN2A/B* status from the methylation data [4]. Two investigators examined CNV traces highlighting the *CDKN2A/B* site [10] to identify either focal *CDKN2A/B* deletions or chromosome 9p loss (Fig. 1a); the senior author adjudicated any inter-rater discrepancies. We used R [RRID:SCR_021094] to analyze recurrence-free survival (RFS) and statistics.

Thirty-eight tumors (4.9%) showed partial or complete loss of *CDKN2A* and/or *CDKN2B*. Considering only the 659 tumors for which we had clinical data [1, 4], 28 (4.2%) showed partial or complete loss of *CDKN2A*, *CDKN2B*, or both. Of these 28, 11 tumors showed homozygous loss of both genes, 15 showed heterozygous loss of both, and two tumors had homozygous loss of *CDKN2A* with heterozygous *CDKN2B* loss (Supplementary Table 1 online resource). Although tumors with any loss of *CDKN2A/B* were more proliferative, less likely to be primary tumors, and more likely to recur, they appeared in all three WHO grades (Fig. 1b, Supplementary Fig. 1, Supplementary Table 2). Molecular classification, however, showed that *CDKN2A/B* losses were almost exclusive to Group C, excepting one primary skull base tumor with heterozygous *CDKN2A/B* loss classified as MenG A. This tumor came from a 62-year-old woman who remained recurrence-free at last follow-up (29 months) (Fig. 1b, Supplementary Table S2).

Even in this aggressive class of C tumors, *CDKN2A/B* loss shortened mRFS: the mRFS was 11 months, and no patient with any type of *CDKN2A/B* loss survived more than 73 months without recurrence (Fig. 1c, Supplementary Table 1). Even heterozygous loss reduced mRFS to 25 months.

Without examining other causes of gene dysfunction, such as single nucleotide variants [5], we may have missed some instances of reduced CDKN2A and/or B protein activity. Nonetheless, deletions involving *CDKN2A/B* were rare even in this sizeable cohort, consistent with previous reports [9], and homozygosity was even more rare. We therefore propose that the most pragmatic course would be to first identify Group C tumors—50% of which will recur by 47 months (Fig. 1c)—and then analyze *CDKN2A/B* status to refine the prognosis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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Data availability

Data used in this study is available in the Gene Expression Omnibus database, https://ncbi.nlm.nih.gov/geo, under the following accession numbers: from GSE84465, GSE136661, GSE183656, GSE101638, GSE101638, GSE139652, GSE180061 and from the authors by request.

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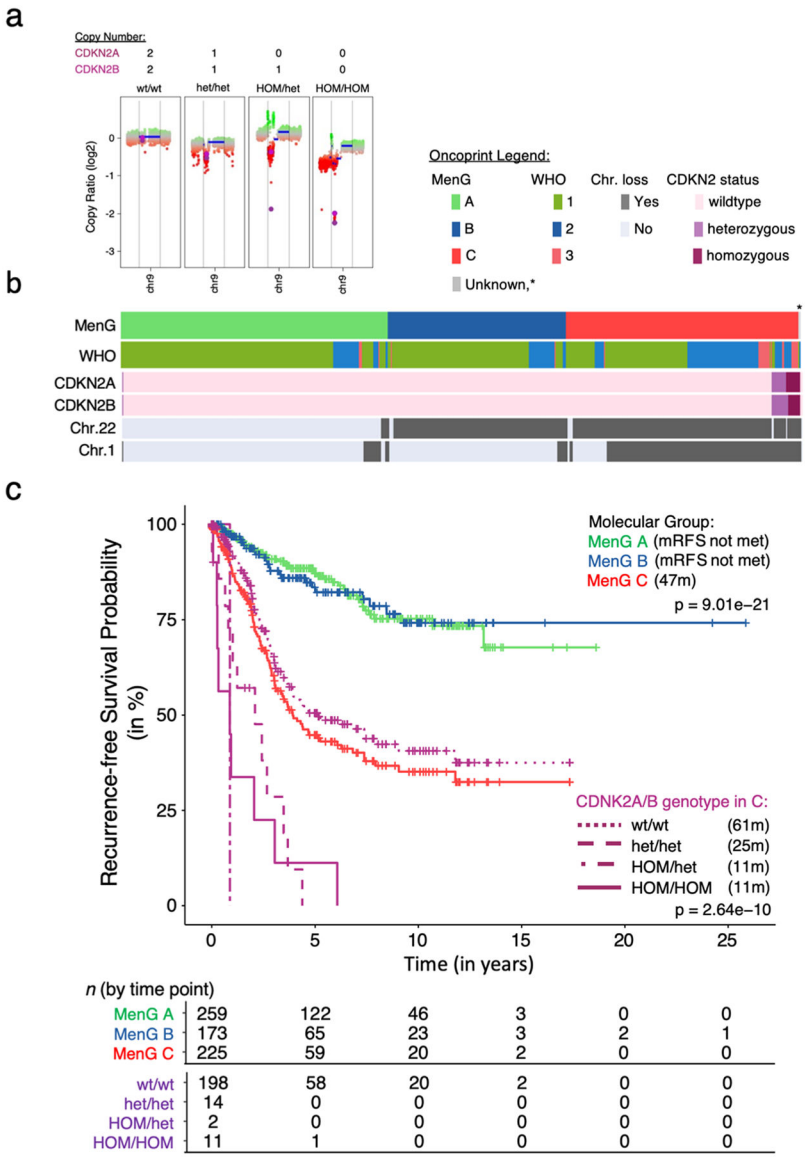

Fig. 1.

CDKN2A/B heterozygous loss shortens RFS. **a** CDKN2A/B scoring based on copy number counts of CNV traces. **b** Oncoprint of the 659 tumors with clinical data, clustered by molecular Groups. The asterisk marks the nonrecurrent tumor that had CDK2A/B loss. **c** Median RFS by molecular group and CDKN2A/B status within Group C, omitting two unclassifiable tumors and the nonrecurrent group A tumor. mRFS in months of each group in parenthesis. Kruskal–Wallis ANOVA by group as well as genotype