Alterations in the RB1 pathway in low-grade diffuse gliomas lacking common genetic alterations

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Author(s) Kim, Young-Ho; Lachuer, Joel; Mittelbronn, Michel; Paulus, Werner; Brokinkel, Benjamin; Keyvani, Kathy; Sure, Ulrich; Wrede, Karsten; Nobusawa, Sumihito; Nakazato, Yoichi; Tanaka, Yuko; Vital, Anne; Mariani, Luigi; Ohgaki, Hiroko
Author(s) at UniBasel Mariani, Luigi ;
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We recently reported that the vast majority (>90%) of low-grade diffuse gliomas (diffuse astrocytoma, oligoastrocytoma and oligodendroglioma) carry at least one of the following genetic alterations: IDH1/2 mutation, TP53 mutation or 1p/19q loss. Only 7% of cases were triple-negative (ie, lacking any of these alterations). In the present study, array comparative genomic hybridization (CGH) in 15 triple-negative WHO grade II gliomas (eight diffuse astrocytomas and seven oligodendrogliomas) showed loss at 9p21 (p14(ARF) , p15(INK4b) , p16(INK4a) loci) and 13q14-13q32 (containing the RB1 locus) in three and two cases, respectively. Further analyses in 31 triple-negative cases as well as a total of 160 non-triple-negative cases revealed that alterations in the RB1 pathway (homozygous deletion and promoter methylation of the p15(INK4b) , p16(INK4a) and RB1 genes) were significantly more frequent in triple-negative (26%) than in non-triple-negative cases (11%; P = 0.0371). Multivariate analysis after adjustment for age, histology and treatment showed that RB1 pathway alterations were significantly associated with unfavorable outcome for patients with low-grade diffuse glioma [hazard ratio, 3.024 (1.279-6.631); P = 0.0057]. These results suggest that a fraction of low-grade diffuse gliomas lacking common genetic alterations may develop through a distinct genetic pathway, which may include loss of cell-cycle control regulated by the RB1 pathway.
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