

Abstract

Little is known about the genetic and molecular events leading to the early stages of human astrocytoma formation. To examine this issue, we analyzed the significance of sequential accumulation of two somatic point mutations (R267W and E258D) in the TP53 gene during the initiation of astrocytoma in a patient born with a single germ-line p53 point mutation (R283H). We adapted a p53 transcriptional assay in yeast to establish the temporal occurrence and allelic distribution of the p53 mutations present in the patient and characterized these mutations through functional assays and structural modeling. Our results show that the first somatic mutation occurred at codon 267 on the p53 allele harboring the germ-line mutation R283H, whereas the second somatic mutation occurred in the remaining wild-type (wt) allele at codon 258. These two mutations induced the formation of tumor cells with the genotype p53(267W+283H/258D), which comprised 70% of the cells in the primary WHO grade II astrocytoma. Another 8% of cells within the tumor had the partially mutated genotype p53(267W+283H/WT) and represented the remnants of a clinically undetectable intermediate stage of astrocytic neoplastic transformation. The remaining 22% of cells had the constitutive p53(283H/WT) genotype and likely consisted of nontumor cells. Functional analysis of the p53 alleles present in the patient's tumor indicated that the germ-line p53(R283H) could transactivate the CDKN1A((p21, WAF1, cip1, SDI1)) but not the BAX gene and retained the ability to induce growth arrest of human glioblastoma cells. The p53(R267W+R283H) and p53(E258D) were incapable of transactivating either promoter or inducing growth arrest.

Modeling of p53 interaction with DNA suggests that R283H mutation may weaken the sequence-specific interaction of p53 lysine 120 with the BAX gene but not the CDKN1A p53-responsive elements. Taken together, these results have characterized, for the first time, the genetic events defining a clinically undetectable precursor lesion leading to a grade II astrocytoma. They also suggest that astrocytoma initiation in this patient resulted from monoclonal evolution driven by a sequential loss of proapoptotic and growth arrest functions of p53.

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