Cancer Genetics

AB109. Novel constitutional and somatic *RB1* mutations underlying retinal cancers in addition to *TNFα*, *KIF13A* and *MGMT* alterations

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Background: Retinoblastoma (RB) is a rare childhood malignant disorder caused by the biallelic inactivation of *RB1* gene. However, the mechanisms that enable RB cells to acquire the additional hallmarks of cancer are still unknown. Hence, it is postulated that other genetic defects like focal amplification of *MYCN*, *BCOR*, *TNFα* and *OTX2* may be present that drives tumor progression in RB.

Methods: Tumor and blood samples from 7 non-familial unilateral and 4 bilateral (2 non-familial and 1 familial) RB patients were investigated for underlying *RB1* mutational spectrum by Sanger Sequencing and Next Generation Sequencing (NGS). They were further investigated for *TNFα* and *KIF13A* gene amplification and *MGMT* hypermethylation. Functional consequence of all mutations was analyzed in-silico (PROVEAN, Mutation Taster, SIFT and CADD) and compared against population databases (1,000 genomes, EXAC and ESP) and gene locus specific mutation database such as rb1-lsdb and HGMD.

Results: We identified 10 novel *RB1* mutations (3 germline and 7 somatic) which arose sporadically. Family screening showed that the parents did not carry the respective mutations found in probands. The chi square test for independence for novel variants *vs.* known variants; germline *vs.* somatic variants as well as variants present in bilateral *vs.* unilateral cases did not show any statistical significance. In addition to *RB1* mutations, four tumors had both *TNFα* and *KIF13A* amplifications, while one tumor had *TNFα* amplification concurrently with promoter hypermethylation of *MGMT*.

Conclusions: Our study adds to the genetic spectrum of *RB1* mutations, which is important as one of the basis for attributing disease pathogenicity when the same variants are subsequently found in other unrelated patients with similar phenotype. In addition, our findings indicate that other genes may play a potentially supportive role in multistep process of tumorigenesis and disease progression.

Keywords: Retinoblastoma (RB); novel mutation; mutation screening; cancer

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