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Unraveling the RNA world of retinoblastoma

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Abstract

Retinoblastoma is the most common primary intraocular tumor in children. It is the first ever cancer to have a genetic basis where inactivation of RB gene in both the alleles would cause the cancer[1]. Whole genome sequencing, gene expression studies, copy number variation analysis, miRNA expression studies, methylation studies have been carried out to identify the additional mutational events involved in causing retinoblastoma[2]. Here, transcriptome sequencing of retinoblastoma and control retina tissues was carried out to identify unique features in retinoblastoma transcriptome. Transcriptome sequencing of 7 retinoblastoma tumors and 3 control retina tissues was carried out using Illumina HiSeq 2500 platform. The paired end reads were aligned to the reference human genome Feb. 2009 release downloaded from the UCSC database (GRCh37/hg19). The reads were analyzed to identify unique genes expressed in retinoblastoma, fusion transcripts, lncRNA's. To identify fusion transcripts EricScript software pipelines were employed that used genome build hg38 and ensemble version 84. This analysis identified over 100 candidate fusion transcript reads. These reads were further inspected by BLAST analysis to minimize the cases of false positives. We considered only those reads which mapped uniquely to gene 1 and gene 2 as candidate fusion transcripts. BLAST analysis of the identified fusion transcript reads revealed that most of the fusion transcript reads aligned 100% either to pseudogenes or other genes in the family and were regarded as false positives. In total, BLAST analysis identified 22 candidate fusion transcripts – 4 unique to retinoblastoma and 18 common between retinoblastoma and retina. Interestingly, all the identified fusion transcripts were found to occur between two adjacent genes on same genomic strand indicating the possibility of read through gene fusions or transcription-induced chimeras (TIC). Four TIC's (LSG1-TMEM44, C19orf24-CIRBP, DSCAML1-FXYD2 and SLC26A6-UQCRC) found unique to retinoblastoma were verified by PCR in a larger cohort of retinoblastoma and retina tissues. LSG1-TMEM44 fusion transcript was previously shown to be present in a glioblastoma cell line – A172. C19orf24-CIRBP fusion transcript was found in burkit lymphoma. Other two fusion transcripts were found to be novel and not reported elsewhere. This work underscored that the retinoblastoma genome is stable where gross deletions and translocations other than RB1 gene are not common.

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