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Genetic Variation in Cyclin-Dependent Kinase Inhibitor 2A Associated with Increased Pancreatic Cancer Risk

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ABSTRACT

Introduction: Pancreatic ductal adenocarcinoma (PDAC) is associated with an inferior prognosis. Therefore, a focus has been on identifying new biomarkers for early diagnosis and predicting patient survival. Recent studies on the entire human genome have pinpointed prevalent genetic alterations on chromosome 9p21 that heighten the vulnerability to cancer. This study aimed to examine the potential partnership of a genetic variant, rs1333049, in CDKN2A in patients diagnosed with pancreatic cancer. Moreover, genome-wide RNA and microRNA sequencing, bioinformatics, and machine learning approaches were undertaken to identify differentially expressed genes (DEGs), followed by validation in an additional PDAC patient cohort.

Methods and Materials: To identify DEGs, genome RNA sequencing and clinical data from pancreatic cancer patients were extracted from the Cancer Genome Atlas Database. We used Kaplan-Meier analysis of survival curves to assess prognostic biomarkers. Ensemble learning, Random forest, Max-voting, Adaboost, Gradient Boosting Machines (GBM), and Extreme Gradient Boosting were used, and GBM was selected with 100% accuracy for analysis. Additionally, protein-protein interaction, molecular pathways, concomitant expression of DEGs, and correlations between DEGs and clinical data were analyzed. We also evaluated candidate genes and miRNAs, and a combination of these was obtained from machine learning algorithms and survival analysis. The process involved extracting DNA samples from these individuals and utilizing TaqMan real-time PCR for genotyping and gene expression analysis. Logistic regression was employed to evaluate the relationship between risk and genotypes, and all prognostic factors of significance identified in the univariate evaluation were incorporated into the multivariate evaluation.

Results: The machine learning results identified 23 and 5 genes and 7 and 20 microRNAs with negative and positive regulation in PDAC, respectively. Essential genes *BMF*, *FRMD4A*, *ADAP2*, *PPP1R17*, and *CACNG3* had the highest coefficient in the advanced stages of the disease. In addition, the survival analysis showed decreased expression of hsa.miR.642a, has.mir.363, CD22, BTNL9, and CTSW and overexpression of hsa.miR.153.1, and hsa.miR.539, hsa.miR, which was associated with a reduced survival rate of 412 patients. Compared to the patients with PDAC, the control group had a decreased occurrence of a TT genotype at the rs1333049 locus. The latter group of cases with a recessive genetic pattern (GG vs. GC+ CC) showed enhanced susceptibility to promoting PDAC (OR = 1.7; 95% CI: 1.2-2.9; p = 0.04).

Conclusion and Discussion: Our findings indicate that genetic variation in *CDKN2A* was linked to the susceptibility of extending PDAC, suggesting the need for additional research in a broader, multi-center context to approve the possible significance of this gene as a novel indicator for the stratification of PDAC.

Keywords: Adenocarcinoma, Genes, Pancreatic neoplasms

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