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Somatic genetic alterations in pancreatic cancer

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The present study was aimed at evaluating the possible roles of KRAS and CDKN2A genes as prognostic biomarkers in exocrine pancreatic cancers. In the 174 exocrine pancreatic cancer samples, 129 tumors contained KRAS mutations, with 97% (126 tumors) at codon 12. GGT>GAT (60.5%, 78 tumors) mutation at codon 12 were the most common one, followed by GGT>CGT (18.6%, 24 tumors), GGT>GTT (14.7%, 19 tumors). In 98 cases of PDAC tumors, 79 (80.6%) carried KRAS mutations. 97.5% (77 tumors) of the mutations were located at codon 12. GGT>GAT (60.8%, 48 tumors) was the most common one, followed by GGT>CGT (22.8%, 18 tumors) and GGT>GTT (10.1%, 8 tumors). No BRAF mutation was found. Out of 174 DNA samples from tumors, mutations and/or deletions at CDKN2A were detected in 48 (27.6%) tumors, with 15 mutations in 13 (7.5%) tumors and deletions in 36 tumors (20.7%). Out of 98 PDAC samples, Mutations and/or deletions in CDKN2A gene were detected in 28 (28.6%) tumors, with 6 mutations detected in 5 (5.1%) tumors and deletions in 24 (24.5%) tumors.

There was no significant association between KRAS mutations and poor survival (HR: 1.68, 95%CI: 0.95-2.99, p=0.07). However, GGT>GAT at codon 12 showed a statistically significant association with poor survival (HR: 2.09, 95%CI: 1.12-3.87, p=0.02) in exocrine pancreatic cancer. When adjusted for age and gender, GGT>GAT mutation at codon 12 was also significantly associated with poor survival in PDAC (HR: 2.17, 95%CI: 1.04-4.54, p=0.04). CDKN2A mutations/deletions were significantly associated with shorter survival in exocrine pancreatic cancer (HR: 1.82, 95%CI: 1.11-2.98, p=0.02) and PDAC (HR: 1.83, 95%CI: 1.06-3.16, p=0.03). KRAS mutations together with CDKN2A mutations/deletions showed a stong association with poor survival in exocrine pancreatic cancer (HR: 3.01, 95%CI: 1.31-6.92, p=0.01) and PDAC (HR: 2.99, 95%CI: 1.18-7.61, p=0.02).These findings indicates that

GGT>GAT mutations at codon 12 of KRAS may serve as a prognostic biomarker for exocrine pancreatic cancer. CDKN2A mutations/deletions can serve as a prognostic biomarker. KRAS mutations together with CDKN2A mutations/deletions can serve as a better prognostic biomarker than either of them.

Since a large proportion of pancreatic tumors had homozygous deletion at the CDKN2A locus, in this study an attempt has been made to develop a technique for cloning of breakpoints. For this purpose, we used available melanoma cell lines as model. In 182 melanoma cell lines, 50 cell lines were detected with homozygous deletion and 58 cell lines with heterozygous deletion. We successfully cloned breakpoints in five melanoma cell lines using primer approximation multiplex-PCR (PAMP) or inverse PCR. Three melanoma cell lines contained deletions with size of 141 kb, 181 kb, and 2,994 kb, respectively. In a novel finding we detected gene fusion involving MTAP and antisense RNA coding ANRIL. The break-points cloned in cell lines were confirmed in corresponding tumours. We also detected transcripts from the fusion gene, which was subsequently confirmed in additional 14 melanoma cell lines. Additionally, an inversion on chromosome 9p with size of 1,096 kb was found accompanied with a deletion of 320 kb in one cell line. A complicated chromosomal rearrangement was found in one melanoma cell lines, with the telomeric side fused to chromosome 15 and the centromic side fused with chromosome 6.