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Identification of potentially druggable mutations using the liquid biopsy in familial PDAC

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Introduction

The prognosis of patients diagnosed with Pancreatic Cancer (PC) is dismal with a 5 year survival rate of around 5 and the key to improving patient survival in pancreatic cancer is the identification of novel drug targets. The majority of PDAC is of a sporadic nature and is thought to arise due to environmental factors such as smoking. However, around 15% of cases appear to have a genetic basis and are classed as Familial Pancreatic Cancer (FPC). KRAS is activated in around 90% of sporadic primary tumors, thus limiting the use of targeted therapies such as BRAF and EGFR inhibitors in this disease. The genetic background of PDAC cases would theoretically condition the spectrum of somatic mutations in primary tumors. Indeed, some of these mutations may have a pharmacological target and provide an alternative treatment in this sub-group of cases.

Objectives

Explore the genetic basis of familial pancreatic cancer and characterize the somatic mutations in primary tumors using the liquid biopsy.

Methods

PDAC cases were recruited to the Spanish Familial Pancreatic Cancer national registry (PanGen-FAM) and information on the family history of cancer was collected. 33 cases from 32 families were screened for a pathogenic mutation in 34 previously described familial cancer or pancreatitis risk factor genes. A sequencing panel was designed using the SureSelect kit from Agilent and sequencing data was analyzed using the ingenuity software. Mutations/variations with a known pathogenic role were selected after excluding common SNPs. Potentially pathogenic mutations/variations were validated by Sanger sequencing in the index case as well as unaffected family members. cfDNA was isolated from plasma using commercially available kits from Qiagen and Promega. KRAS mutations were identified by BEAMing and sequencing analysis of cfDNA was performed using the TruSight kit from Illumina.

Results

A potentially pathogenic germline mutation was identified in 7/22 (31%) FPC families, 8/11 (73%) HBOC+PC families and in 2/3 (66%) families with other cancer syndromes with cases of PC. BRCA 1, BRCA2, ATM and CHEK mutations were associated with the HBOC and PC syndrome whereas, mutations in MLH1, MUTYH and MSH2 were associated with FPC families that did not fulfill criteria for other cancer syndromes. In addition, potentially pathogenic mutations were found in 4/10 (40%) cases with an unusually early onset of disease at less than 50 years of age. KRAS and p53 mutations were the most frequent mutations found in cfDNA from sporadic cases by BEAMing and sequencing analysis, whereas BRAF, EGFR and KIT mutations were found in a sub set of familial cases.

Conclusions

A large majority of families at high risk of pancreatic cancer harbor pathogenic mutations in previously described familial cancer genes. The frequency of potentially druggable mutations was greater in cases with a familial background. The genetic background of these cases conditions the spectrum of somatic mutations in the primary tumors which is different to those mutations found in sporadic cases. Sequencing of cfDNA and the identification of druggable mutations in familial cases provides a strategy for personalized medicine in this sub group of PDAC cases.