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Advances in the genetics and phenotype of familial pancreatic cancer

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State-of-the-art and objective

Pancreatic ductal adenocarcinoma (PDAC) has a poor prognosis, resulting in a 7.2% 5-year survival rate. Approximately 10-15% of PDAC cases cluster in families, with a suspected hereditary or familial background. Familial pancreatic cancer (FPC) is defined as a family with at least two affected first-degree relatives with no known genetic cause. The Spanish familial pancreatic cancer registry (Pan-Gen-FAM) was established in 2009 with the principal objective to characterize the phenotypic and genetic background of FPC.

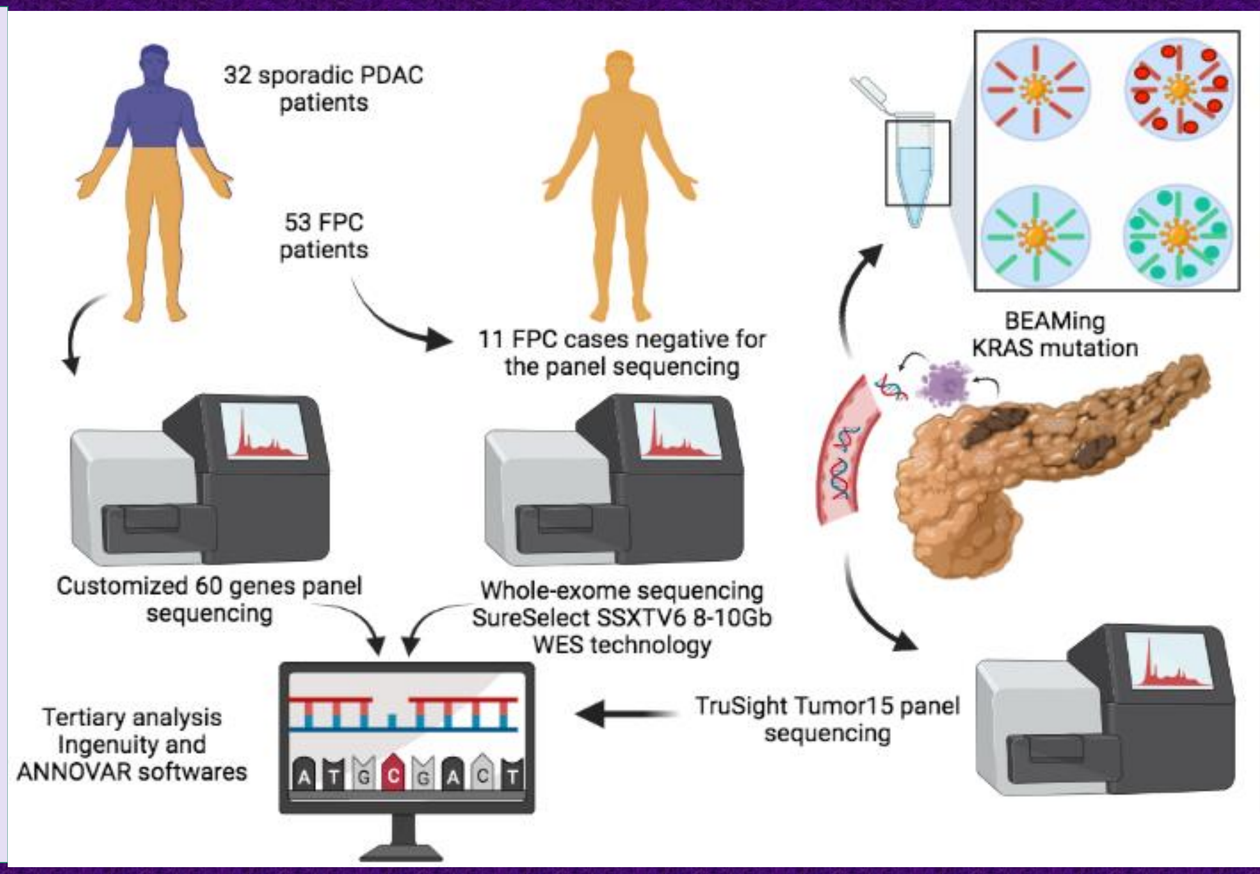
In this study, the germline mutation profile of familial and sporadic PDAC cases was analyzed with the aim to determine the genetic cause of FPC. Furthermore, the somatic mutation profile of PDAC cases was determined in diagnostic plasma samples to identify somatic mutations that can be exploited in the clinic. Due to the limited availability of primary tumor tissue in PDAC, the liquid biopsy is an ideal surrogate to study somatic alterations.

Material and methods

Panel sequencing of germline DNA was performed on 60 genes associated with hereditary cancer and carcinogenesis using the Sureselect technology (Agilent) in 85 PDAC cases: 53 from families with an apparent hereditary pancreatic cancer syndrome and 32 cases with sporadic PDAC.

Exome sequencing was performed in 11 PDAC cases from FPC families that were negative for a germline mutation in known familial cancer genes. Ingenuity Variant Analysis and ANNOVAR tools were used to identify potentially pathogenic variants related to PDAC risk, allele fraction and call quality filtering excluded false positives and common variants. Variants with a predicted pathogenic or likely pathogenic effect (nonsense, frameshift, damaging missense, canonical splice site variants and an inferred gain or loss of function) were retained and validated via Sanger sequencing.

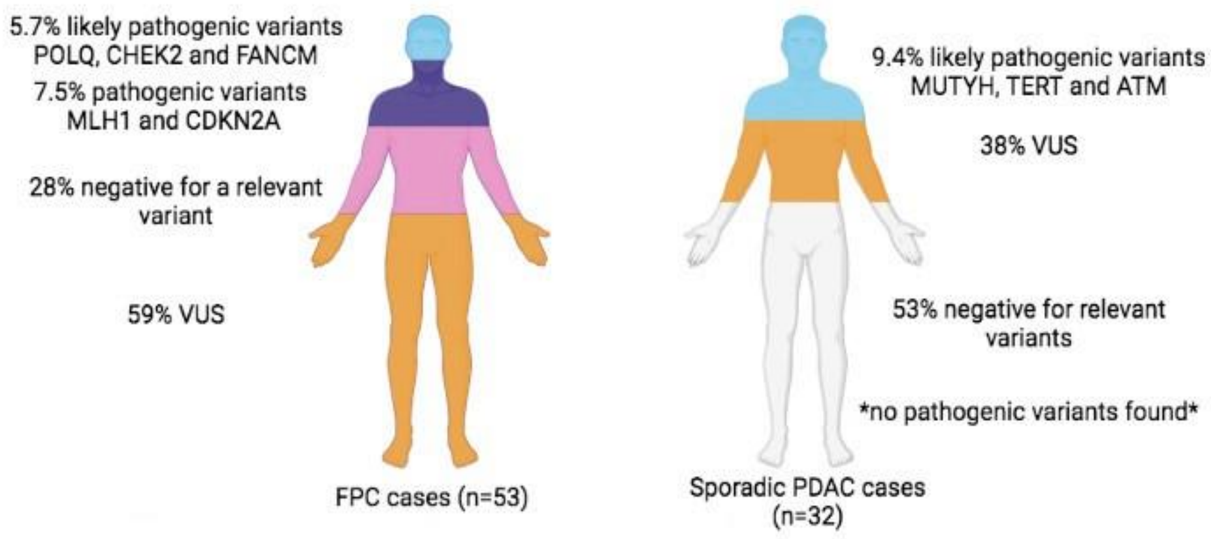
The somatic mutation profile of familial or hereditary vs sporadic PDAC cases was tested via BEAMing (KRAS mutations) and panel sequencing using the TruSight15 technology (Illumina). Furthermore, clinical parameters of the cases such as disease stage and overall survival were analyzed between FPC and sporadic cases via the Mann-Whitney and Chi square tests and the Kaplan Meyer and log Rank tests.



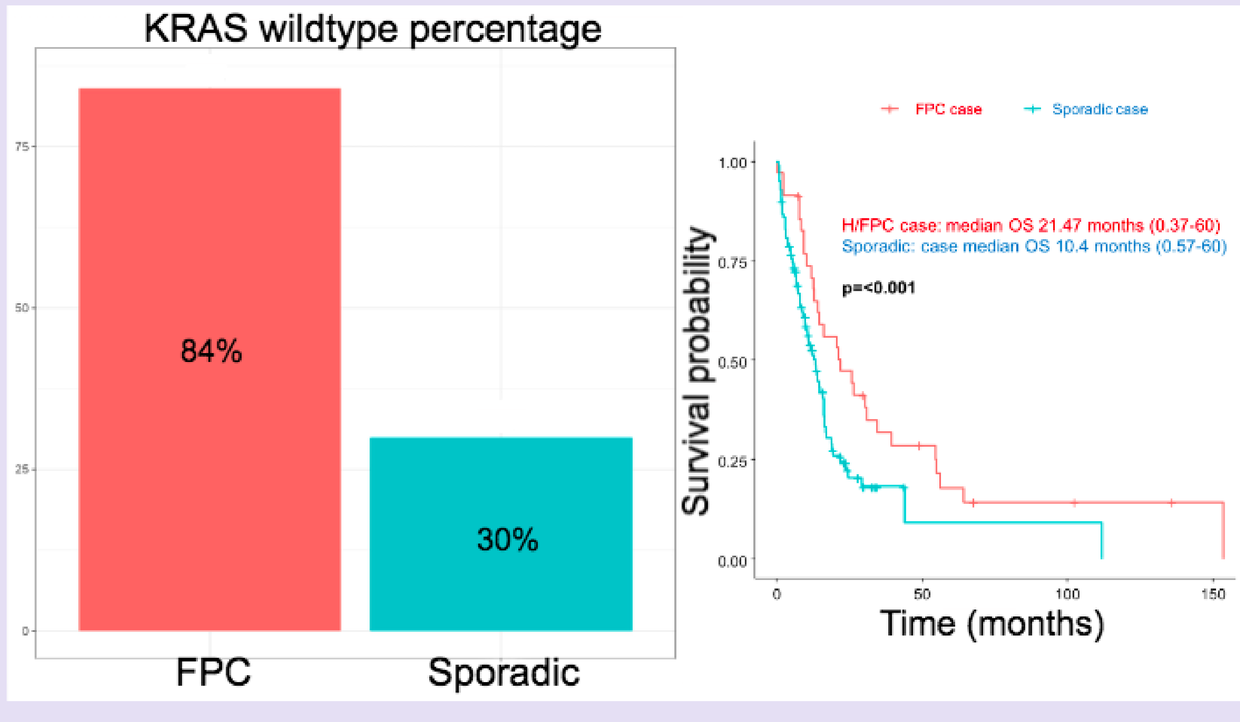
Results

Among 53 FPC cases we have identified, via panel sequencing, pathogenic variants with a previously described role in PDAC risk only in 4 individuals (7.5%) in MLH1 and CDKN2A genes and none of the sporadic cases. Likely pathogenic variants have been found in 5 FPC cases (5.7%) in POLQ, CHEK2 and FANCM and in 3 sporadic cases (9.4%) affecting MUTYH, TERT and ATM genes. Variants of unknown significance (VUS) were found in 59% and 38% of FPC and sporadic cases, respectively. 28% of FPC cases were negative for a relevant variant compared with 53% of sporadic cases.

Missense variants with a damaging effect were found in all 11 PDAC that underwent exome sequencing. Stop gain, stop loss or frameshift variants were validated in 5 FPC cases, affecting WWOX, C2orf83, CYP3A5 and TANGO2. Some of these genes have relevant roles in cancer development, for example, WWOX is tumor suppressor gene and CYP3A5 is involved in drug metabolism.



The majority of hereditary or familial PDAC cases (84%) were negative for a KRAS somatic mutation compared with 30% of sporadic cases. Furthermore, familial or hereditary cases have a longer overall survival compared to sporadic cases (10.2 vs. 21.7 months, respectively). Finally, we show that KRAS mutation negative cases harbor somatic mutations in potentially druggable genes such as KIT, PDGFR, MET, BRAF and PIK3CA that could be exploited in the clinic.



Conclusions

The genetic basis of familial pancreatic cancer can be explained in some cases by previously described hereditary cancer genes such as MLH1 and CDKN2A. The majority of sporadic cases are negative for high-risk germline mutations, as expected. However, there may be some mis-classification of FPC and sporadic cases due to an inaccurate recall of family history. Furthermore, validation in larger cohorts is needed to determine the pathogenicity of VUS variants found in both cohorts. Here we demonstrate that there FPC and sporadic cases are different at the level of germline and somatic mutations, that could be potentially exploited in the clinic. Furthermore, FPC cases have a better OS compared with sporadic cases, even though all PDAC patients are currently treated the same in the clinic, with cytotoxic agents in the majority of cases.