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POSTER ID:

Molecular characterization of familial pancreatic cancer through NGS and liquid biopsy

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State-of-the-art

Pancreatic ductal adenocarcinoma (PDAC) is the third leading cause of death in EU and US, with a 5-year overall survival rate of 7.2%. More than 90% of PDAC are mutant KRAS, they are therapy resistant and the only cure option is a surgical resection, but only 20% of cases are diagnosed at a resectable stage.

Up to 15% of PDAC cases have familial aggregation with an unknown genetic basis, known as familial pancreatic cancer (FPC). FPC is defined as a family with at least two PDAC affected first-degree relatives with unknown genetic cause.

The Spanish familial pancreatic cancer registry (PanGen-FAM) was established in 2009 with the principal objective of characterizing the phenotype and genetic background of FPC, as only 10-13% of families carry described germline mutations in well known genes, associated with other hereditary syndromes.

Objective: To determine de genetic basis of FPC and validate biomarkers using liquid biopsy for early detection of PDAC.

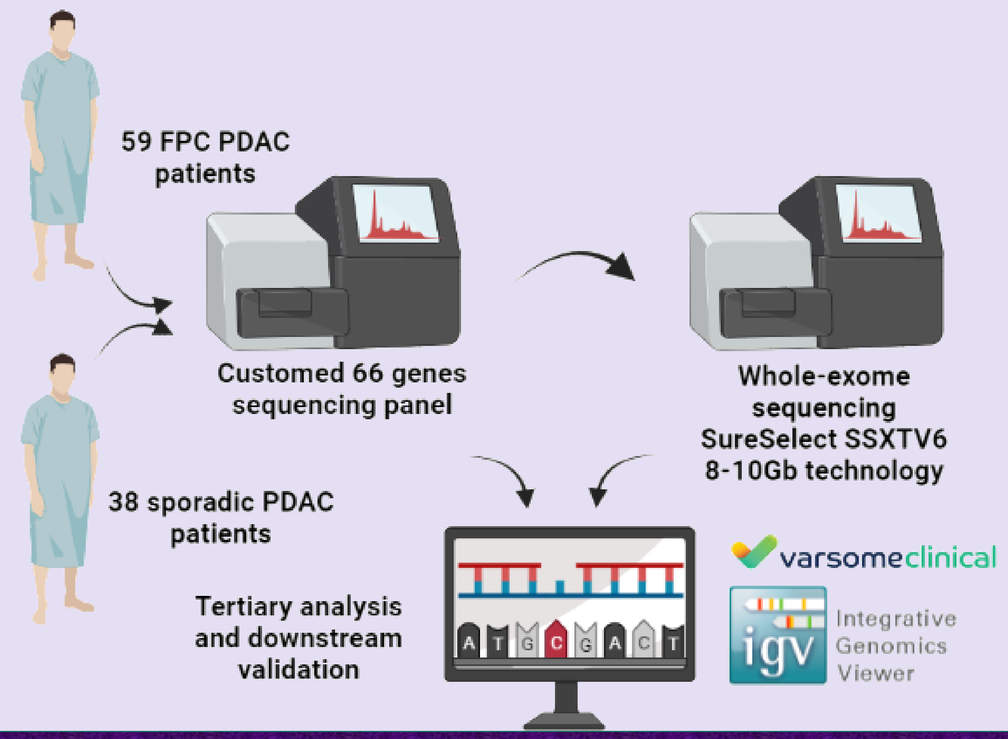
Material and methods

Germline variant identification was performed using a 66 gene custom sequencing panel (Agilent Tech) in a cohort of 97 cases (59 with an apparent FPC syndrome and 38 sporadic PDAC cases).

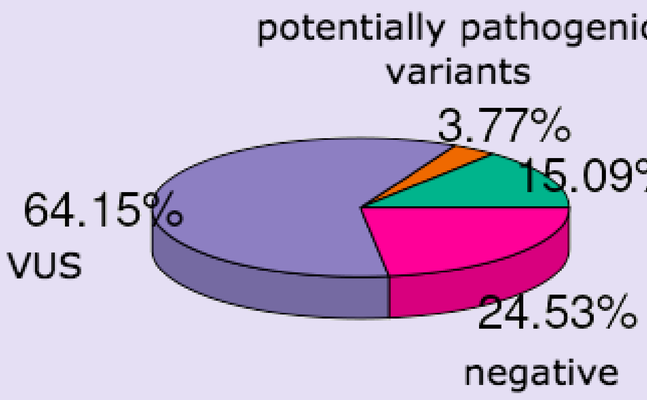
Those negative cases (no interesting variants found in panel sequencing) were selected for exome sequencing (Illumina) (n=27).

Tertiary analysis was performed using Varsome Clinical platform and IGV software, and variants were filtered according to our call quality, impact and population frequency criteria.

cfDNA levels were explored in the liquid biopsy of PDAC cases, high-risk individuals from FPC families and healthy controls as biomarkers for early detection.

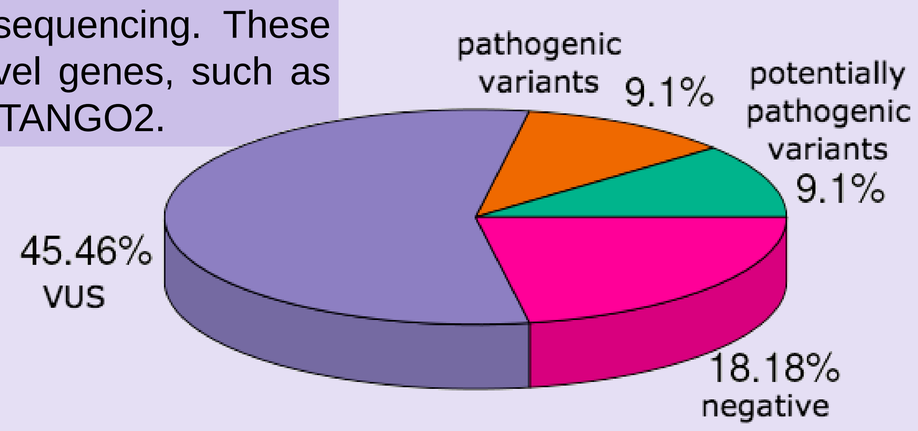


Results

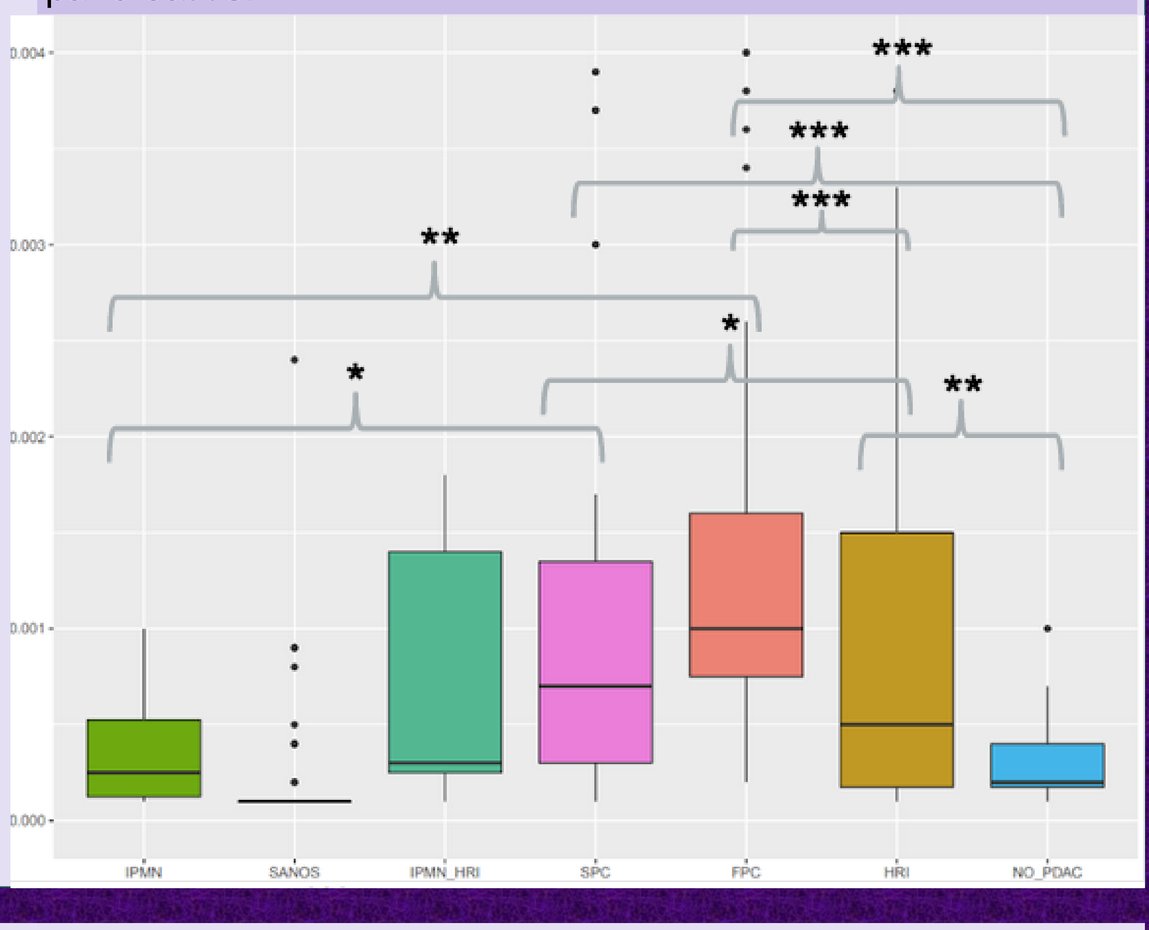


Panel sequencing revealed that 19% of FPC cases carried pathogenic or likely pathogenic variants in known cancer risk genes (MLH1, CDKN2A and POLQ, CHEK2 and FANCM).

Via **exome sequencing** there were found pathogenic or likely pathogenic variants in 18% of FPC cases that were negative for panel sequencing. These variants affected novel genes, such as WWOX, CYP3A5 or TANGO2.



cfDNA levels in plasma were significantly higher in PDAC cases compared to healthy controls, high-risk individuals, and other pancreatic lesions, such as IPMN, pNETs, or chronic pancreatitis.



Conclusions

- Targeting sequencing and exome analysis of FPC families reveals that this population carry multiple variants in DNA repair and tumor suppressor genes that could play a role in pancreatic cancer risk.
- Molecular characterization of PDAC patients could improve their classification and they could benefit from targeted therapies.
- cfDNA based markers are potential diagnostic markers for early detection of PDAC.

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