Exome sequencing of familial pancreatic cancer cases identifies pathogenic and potentially pathogenic germline variants

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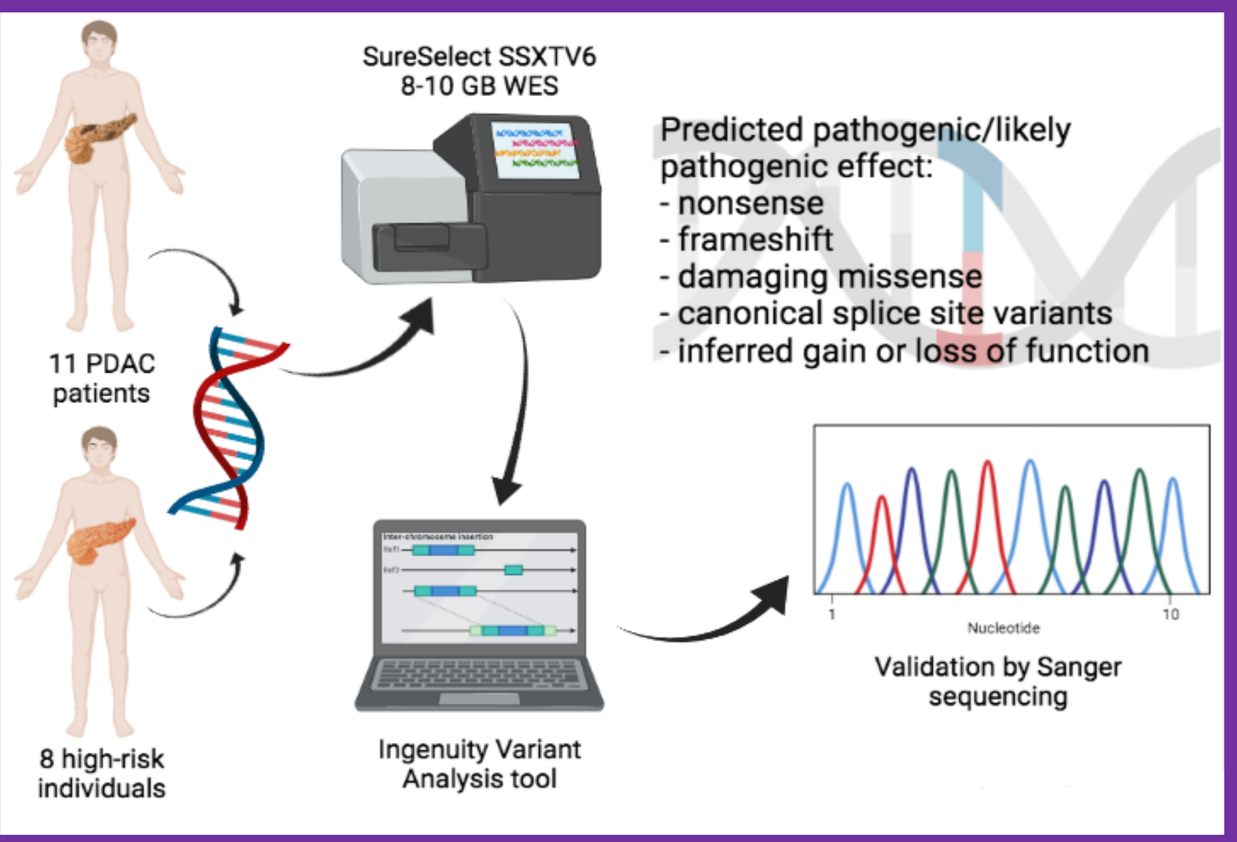
State-of-the-art and objective

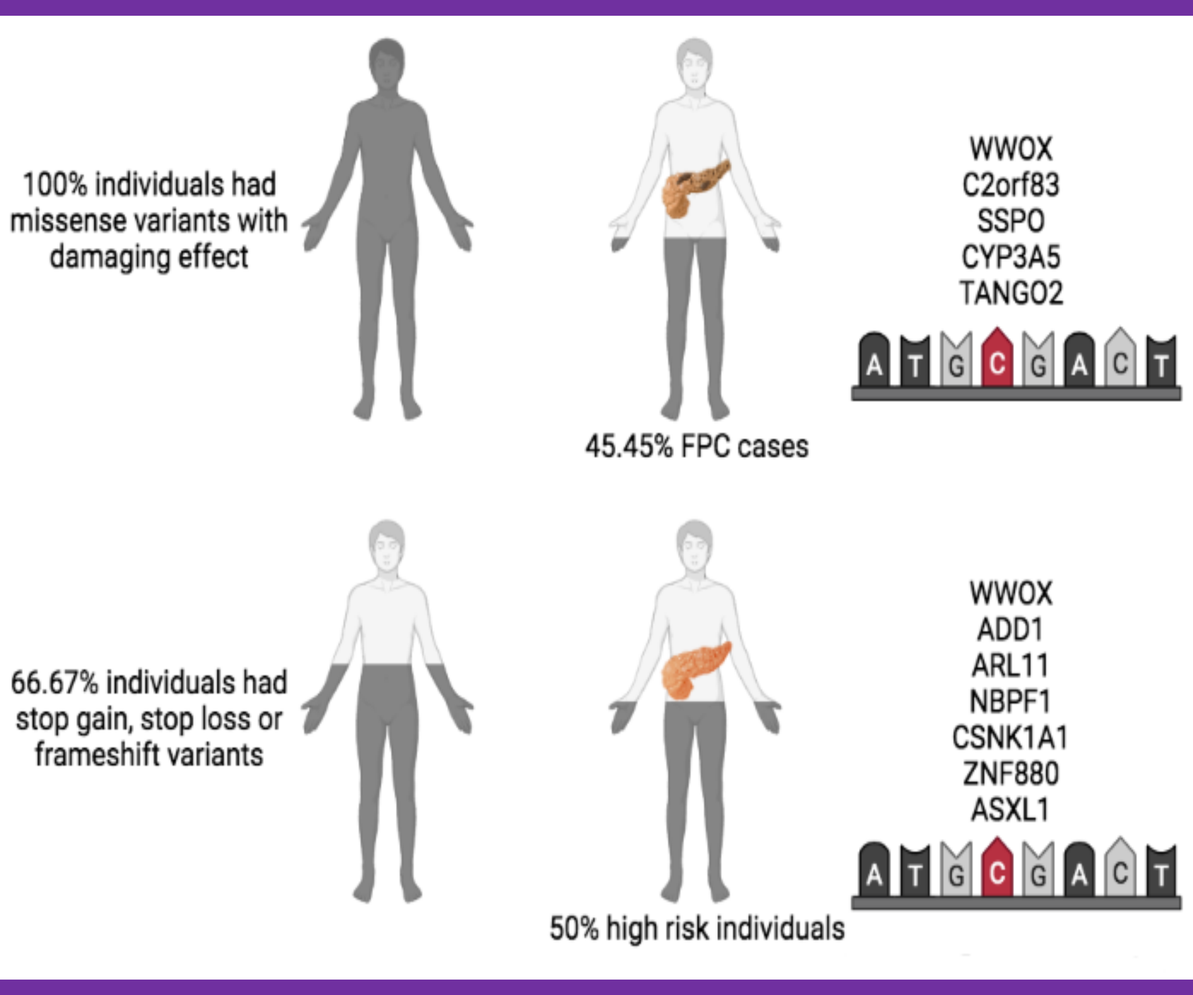
Pancreatic ductal adenocarcinoma (PDAC) has a poor prognosis in spite of recent advances in therapeutics. Most patients are diagnosed at an advanced stage resulting in a 7.2% 5-year survival rate. 10-15% of PDAC cases cluster in families with an unknown genetic basis, known as familial pancreatic cancer (FPC). Exome sequencing of FPC cases and high-risk individuals was performed to identify new variants related to PDAC risk.

Material and methods

11 PDAC cases and 8 healthy high-risk individuals from FPC families were selected for exome sequencing, as they were negative for a germline mutation in known familial cancer genes. Genomic DNA was isolated (Flexigene DNA kit) and the exome sequencing was performed using the SureSelect SSXTV6 8-10Gb WES technology.

Ingenuity Variant Analysis tool was 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.

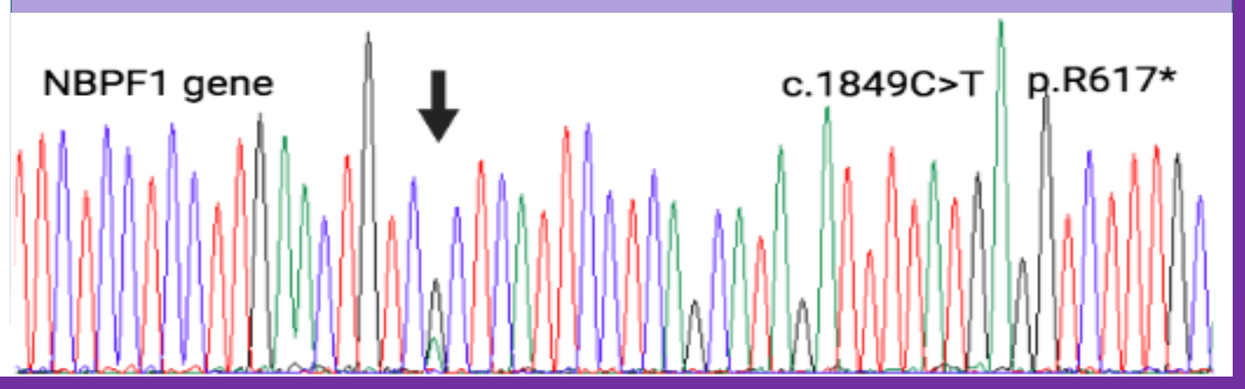




Results

Missense variants with a damaging effect were found in all the individuals, but only 14 (66.67%) had stop gain, stop loss or frameshift variants. These variants were validated by Sanger sequencing in 5 FPC cases (45.45%), affecting WWOX, C2orf83, SSPO, CYP3A5 and TANGO2 and 4 high-risk individuals (50%) with variants in WWOX, ADD1, ARL11, NBPF1, CSNK1A1, ZNF880, ASXL1 genes.

Some of these genes have relevant roles in cancer development, WWOX, ARL11 and NBPF1 are tumor suppressor genes; CSNK1A1 regulates cell cycle and CYP3A5 is involved in drug metabolism.



Conclusions

- Some cases classified as FPC lacked relevant germline mutations via targeted and exome sequencing.
- PDAC aggregation in these families may be due to multiple low penetrance missense variants. Alternatively, these patients may have been misclassified as FPC due to an inaccurate recall of family history.
- Validation in larger cohorts is needed to determine the specific potential and penetrance of the significant variants found.

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