GENETICS AND GENOMICS OF PANCREATIC CANCER IN ITALIAN PATIENT COHORTS

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Introduction

Pancreatic ductal adenocarcinoma (PDAC), with a five-year survival rate of less than 10%, is expected to become the **second most prevalent cause of cancer-related mortality** in both the US and Europe by 2030. About **10%** of cases have a **family predisposition**; however, the heritability of pancreatic cancer may be twice as much. Only **10–20%** of patients have **resectable disease** and **local and distant relapses** are frequent. In most cases, **conventional therapies** such as chemotherapy and immunotherapy **fail** to provide **long-term benefits**, underlining the **pressing need for innovative approaches** to improve the clinical management of this deadly disease.

Objectives

This **research project aims** to combine different "**omics**" (genomics/transcriptomics/epigenomics) to **study pancreatic cancer tumorigenesis** by using **second** and **third-generation sequencing technologies** and **patient-derived organoids**. This approach will enable the exploitation of cancer vulnerabilities and expand the repertoire of drug targets to the undruggable genome.

Methods

Schematic Overview of the Experimental Workflow

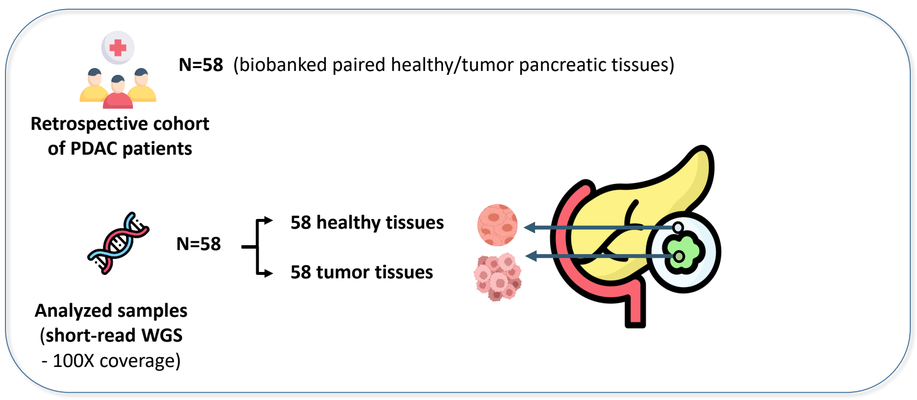
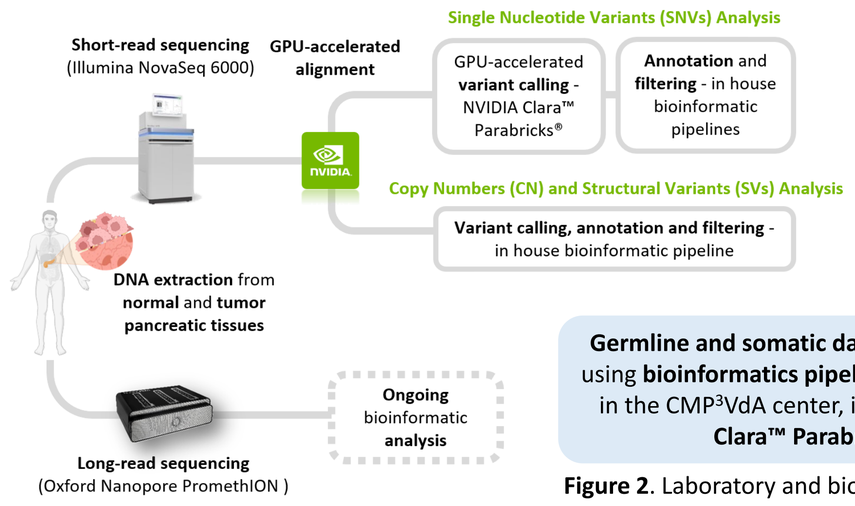


Figure 1. Pilot study design: retrospective cohort of patients with pancreatic cancer.



Germline and somatic data were **analyzed** using **bioinformatics pipelines** implemented in the CMP³VdA center, including **NVIDIA Clara™ Parabricks®**

Figure 2. Laboratory and bioinformatic workflow.

Results

Genetics and Genomic Landscape of PDAC

1. Somatic variants analysis

Tumor genomic landscape of somatic variants in 58 PDAC patients

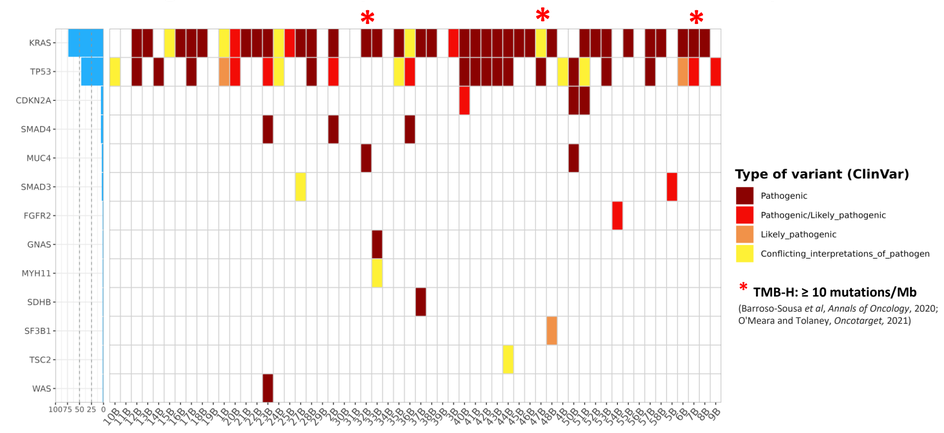


Figure 3. Waterfall plot reporting variants classified as P/LP and CI of P by Clinvar.

Percentage of mutations identified in key pancreatic cancer genes in the PDAC cohort

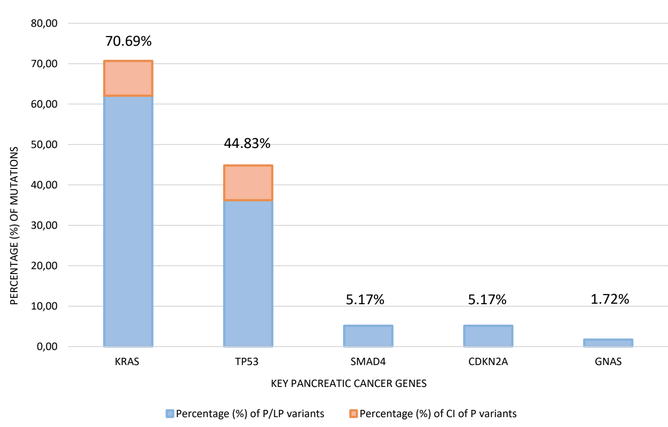
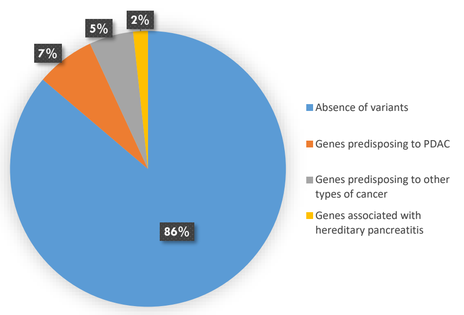


Figure 4. Histogram displaying the percentage of P/LP and CI of P variants in key pancreatic cancer genes.

Frequencies of somatic variants in key pancreatic genes ***KRAS***, ***TP53***, ***SMAD4***, ***CDKN2A*** and ***GNAS*** recapitulate the trend observed in different PanCancer cohorts

2. Germline predisposing variants



BRCA2:c.8303_8304delTT (LP, AD)
ATM:c.4396C>T (P, AD)
CHEK2:c.1427C>T (LP, ?)
MLH1:c.50A>T (VUS/LP, AD/AR)
ATM:c.9047_9057delAACTGAAAGGA (P, LP, AD)

CFTR:c.350G>A (P/LP, AD)
CFTR:c.3154T>G (LP/VUS, AD)
CFTR:c.3485G>T (LP/VUS, AD)

ERCC3:c.325C>T (P, AR)
MUTYH:c.1356_1358delGGA (P/LP, AR)
MSR1:c.818-1G>A (LP, ?)
RNASEL:c.793G>T (P, AD)
USP8:c.3037C>T (LP, ?)

Figure 5. Germline variants in PDAC cohort.

14% of patients (**8/58**) show **germline P/LP variants** in **genes predisposing** to **PDAC**, **other** types of **cancer** and **hereditary pancreatitis**

3. Structural variants analysis with a focus on chromothripsis events

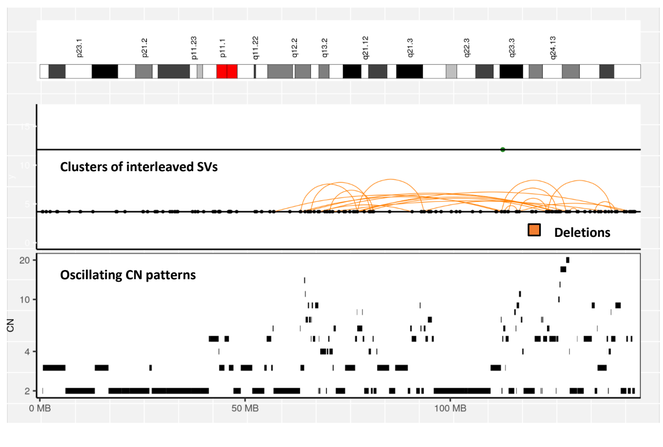


Figure 6. Chromothripsis event on chr. 8: cluster of interleaved SVs and a CN profile oscillating between different states. Ploidy status: 3.18.

In depth analysis of **chromothripsis events** with high confidence is **ongoing** on the **entire PDAC cohort**

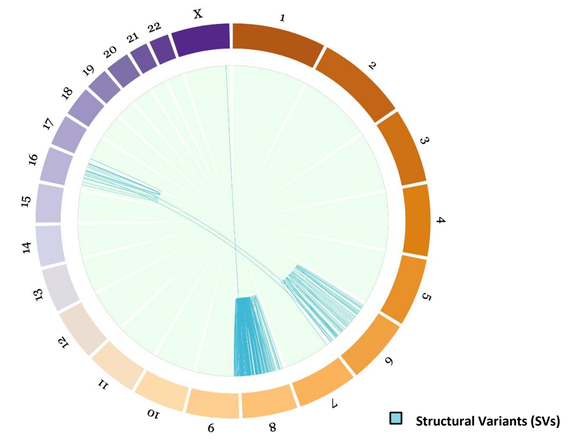


Figure 7. Circos plot including structural variants on chromosomes 6, 8 and 16.

Circos plot showing the **genome-wide profile of rearrangements** in selected chromosomes (chr. 6, chr. 8, chr. 16)

Conclusions and Future Perspectives

- ❑ **Germline actionable P/LP variants** are identified in ~**9%** of patients and a **genetic susceptibility** is identified in **14%** of cases.
- ❑ **PDAC somatic genomic landscape is similar** to other **PanCancer cohorts**.
- ❑ **Long-read sequencing** (ONT) on selected samples **is ongoing** to complement short-read sequencing.
- ❑ A **multicenter national prospective PDAC cohort** study is designed to expand the number of PDAC Italian patients.

Contact

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References

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2. Jung K, Lee S, Na HY, Kim JW, Lee JC, Hwang JH, Kim JW, Kim J. NGS-based targeted gene mutational profiles in Korean patients with pancreatic cancer. Sci Rep. 2022 Dec 3;12(1):20937.