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Investigating the genetic predisposition of rare hereditary cancer syndromes via the Hellenic Precision Medicine Network

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BACKGROUND

❖ **Rare hereditary cancer syndromes** caused by pathogenic germline variants confer substantial cancer risk. Identification and precision management of individuals at risk are critical for risk reduction, tailored surveillance, and improved outcomes, making access to genetic testing and counseling essential.

❖ **Current challenges in the clinical genetics landscape in Greece**:

(a) Notable absence of organized genetic centers and a shortage of certified genetic counselors and clinical geneticists.

(b) Limited reimbursement for hereditary cancer genetic testing by national healthcare insurance, with coverage restricted to specific, pre-defined cases. Consequently, patients and their families frequently shoulder the financial burden.

Establishment of the state-funded nationwide Hellenic Network of Precision Medicine (HNPM):

(a) Integrates leading research and academic laboratories, combining diagnostics with advanced research in cancer biomarkers and cancer predisposition.

(b) Establishes accredited biobanks and specialized genetic/molecular analysis units to provide robust infrastructure for both clinical and research needs.

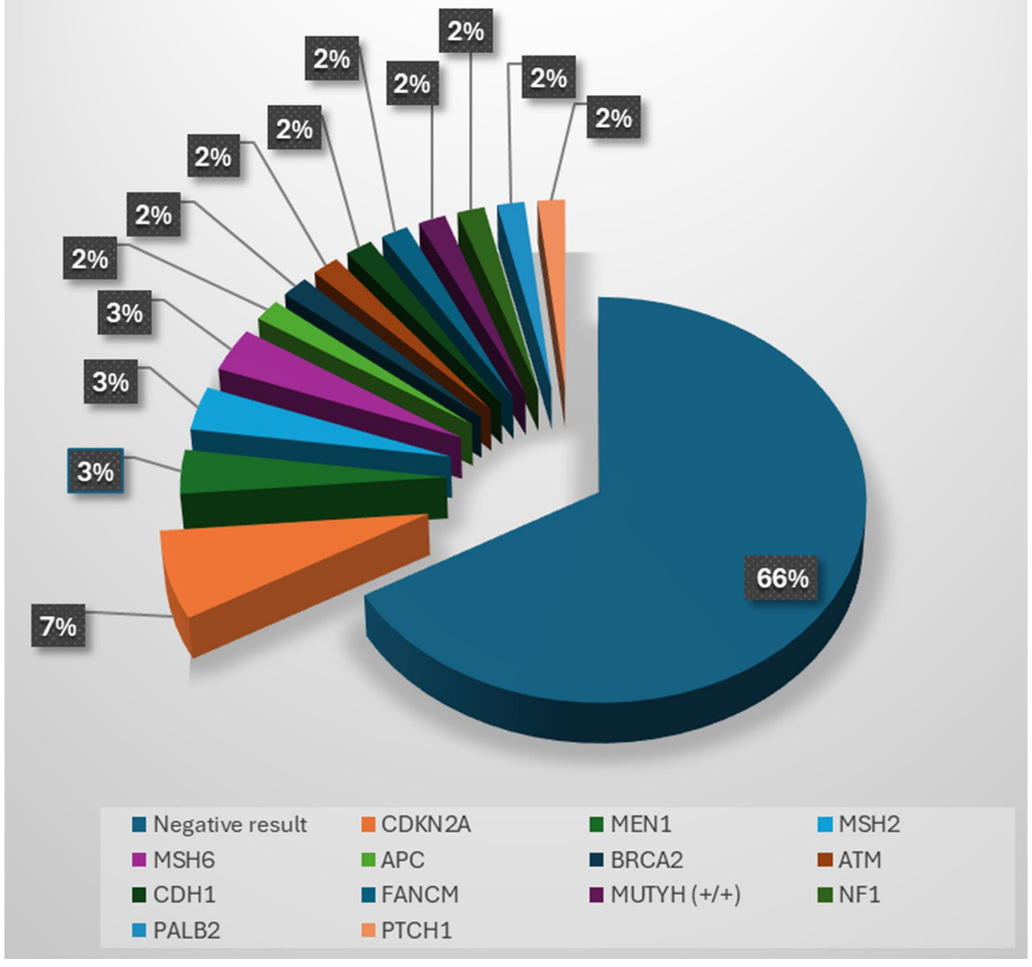
Aim

To elucidate the genetic susceptibility underlying rare hereditary cancer syndromes in Greece, through the HNPM platform, aiming to advance scientific research, guide clinical practice, and ensure access to precision oncology for all patients and families at risk.

Patients and Methods

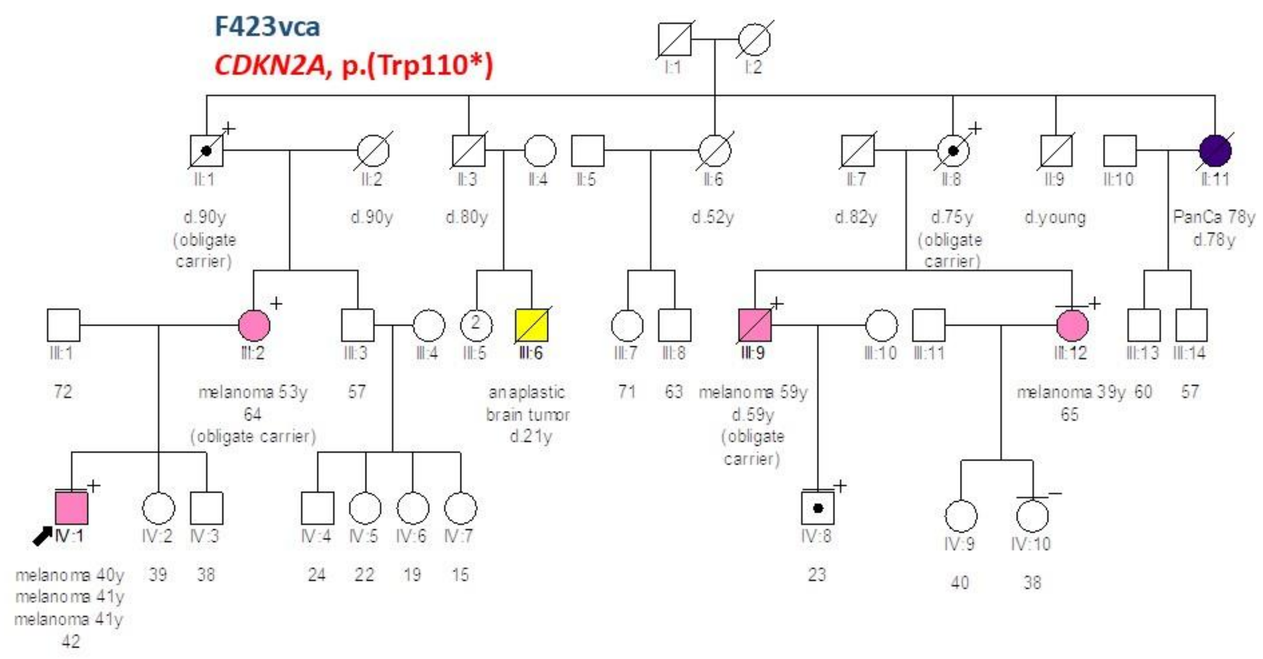
- **Cohort:** A total of 192 patients with malignant/pre-malignant diagnoses fulfilling NCCN (National Comprehensive Cancer Network) guidelines were referred to the Human Molecular Genetics Laboratory, which has served as a reference laboratory in hereditary cancer, over the last 30 years.
- **Diagnoses:** colorectal (30), endometrial (32), gastric (13), melanoma/multiple BCCs (49), multiple primaries (4), ovarian (2), pancreatic (25), prostate (4), renal (8) cancer, rare malignancies (8), neurofibromatosis (4), and pre-malignant manifestations (13)
- **Mean age at diagnosis:** 49.5 years (range 17-80 years)
- **Methods**: Massively parallel sequencing using Illumina's Hereditary Trusight Cancer panel or Sanger sequencing, and MLPA

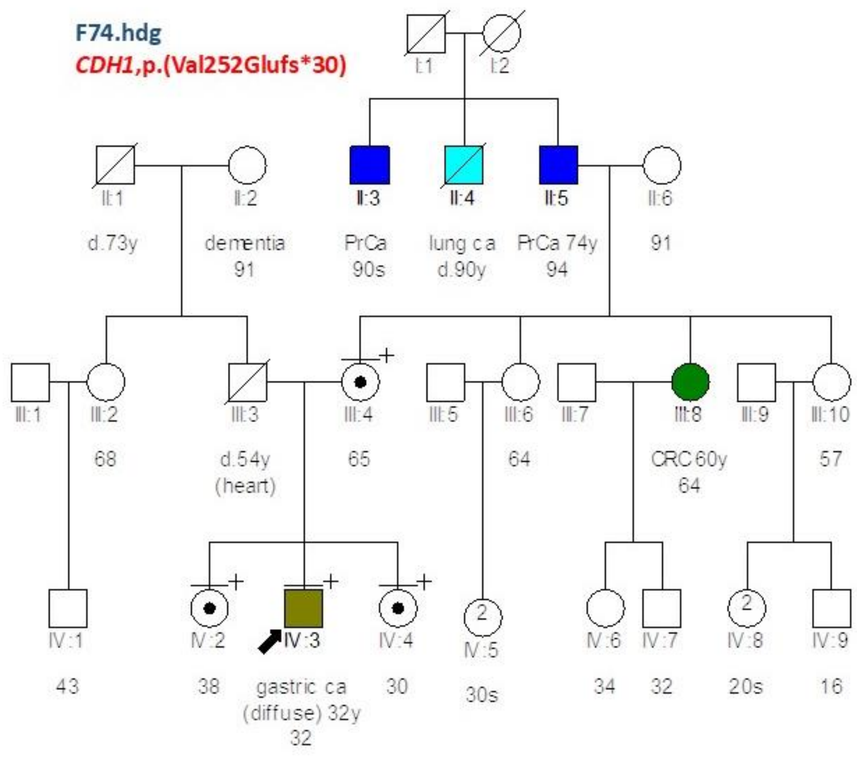
Results



34% (64/192) of patients carry germline pathogenic variants (PVs)

- PVs are distributed in 13 susceptibility genes associated with rare or ultra-rare cancer syndromes
- Variants of unknown significance (VUS) detected in only 1% of cases
- 60% of families have undergone cascade testing for the inherited genetic variant
- 63.2% of carriers reported a positive family history of cancer with hereditary etiology





Conclusions

✓ **One in three** patients with a rare hereditary cancer syndrome carries a loss-of-function variant in a cancer susceptibility gene.

✓ Establishing a **coordinated infrastructure** with specialized laboratories and expert personnel is critical for advancing hereditary cancer genetics in Greece.

✓ By offering **pro bono genetic testing** for hereditary cancer, many rare hereditary cancer cases are promptly identified, paving the way for **personalized treatments and cancer prevention**.

✓ Overall, integrating expertise and accessible genetic services within a **national network** enhances precision oncology and promotes **equitable care** for families at risk.

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