THE CYPRUS INSTITUTE OF NEUROLOGY & GENETICS

Moderate-Risk Variants in High-Risk Breast Cancer Susceptibility Genes

The topic is eligible for the following Programmes:

PhD in Molecular Medicine
PhD in Medical Genetics

Hosting Department:
Biostatistics Department

Contact Persons:
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Mode of Study:
Full Time

Available Funding:
Marie Curie Doctoral Network (36 months) €3,284.19 (gross) plus additional mobility and family allowance (where applicable).

Eligibility Requirements:

- Master's degree or equivalent at the time of starting the PhD contract
- No PhD degree at the time of starting the PhD
- **Mobility rule:** candidates must not have lived, worked, or studied in the country of the recruiting beneficiary for more than 12 months in the 36 months prior to recruitment (any nationality eligible provided the rule is met)

The student is expected to spend few months at QIMR Berghofer in Brisbane Australia (M22 – M25) at the lab of Professor Amanda Spurdle to conduct penetrance analysis of pedigrees for moderate-risk variants to confirm risk levels; bioinformatic analysis for molecular function of "intermediate" variants; mRNA impact assessment for splicing-related variants. The student will also spend two months at Stremble company, Cyprus supervised by A. Antoniades, M30-M31 so they apply their knowledge from research setting and translate them into industry applications, while gaining exposure to industry standards and regulatory processes

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Abstract:
Clinical interpretation of germline variants in high-risk cancer susceptibility genes is currently guided by the ACMG/AMP classification framework and gene-specific recommendations developed by ClinGen-approved Variant Curation Expert Panels. These guidelines were originally designed for Mendelian disorders in which pathogenic variants typically confer high and relatively uniform penetrance. In genes such as BRCA1, BRCA2, and TP53, variant classification has therefore largely relied on comparison with the average features of classical pathogenic variants, including protein-truncating variants and missense variants known to cause loss of function.

However, growing evidence from large international consortia, including ENIGMA, indicates that some variants in high-risk cancer genes are associated with reduced or atypical penetrance. Such variants may confer lower lifetime cancer risk, later age at onset, or altered tumour spectra, and may not satisfy the standard feature specifications used for classical pathogenic variants. As a result, these variants are at risk of misclassification as variants of uncertain significance or (likely) benign, or conversely, of being classified as (likely) pathogenic without recognition of their reduced penetrance. Both scenarios limit the ability to provide risk-adapted clinical management and genetic counselling.

This PhD project aims to systematically investigate reduced and atypical penetrance variants in high-risk cancer susceptibility genes using population-scale genetic and clinical data. By integrating large cohort resources, penetrance estimation, and quantitative molecular and clinical evidence, the project seeks to evaluate the limitations of current classification frameworks and develop penetrance-aware approaches to variant interpretation. The overarching goal is to improve clinical classification practices and support more personalised, risk-adapted recommendations for carriers of germline variants in cancer susceptibility genes.

Project Plan for years 2, 3 & 4:Year 2 — Systematic Characterisation of Reduced-Penetrance Variants:

- Compile a curated catalogue of germline variants in high-risk cancer susceptibility genes (BRCA1, BRCA2, and others as appropriate) with existing or suspected evidence of reduced or atypical penetrance.
- Review ACMG/AMP and ClinGen VCEP criteria applied to these variants and document which evidence categories contribute to uncertainty or discordant classifications.
- Use population-based datasets (e.g. biobank or consortium data, where available) to estimate variant-specific cancer risks, age-at-onset distributions, and tumour characteristics.
- Compare penetrance estimates for reduced penetrance variants with those of classical pathogenic variants within the same gene.

Year 3 — Evaluating and Extending Variant Classification Frameworks:

- Assess how reduced penetrance variants perform against existing ACMG/AMP evidence categories (e.g. population frequency, segregation, functional data).
- Identify systematic patterns leading to misclassification or loss of clinical nuance.
- Develop and test penetrance-aware extensions or decision-support frameworks that incorporate quantitative risk estimates into variant interpretation.
- Explore integration of additional evidence types (e.g. polygenic background, family history modifiers, tumour features) into classification models.
- Synthetic dataset and simulation creation and evaluation

Year 4 — Clinical Interpretation and Translational Implications:

- Apply the developed framework to a broader set of variants and genes to assess generalisability.
- Finalise thesis writing, integrate all results, and prepare manuscripts for submission.
- Present findings at international conferences.