Functional evaluation of PALB2 variants using a BRCA1 and BRCA2 interaction approach

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INTRODUCTION: *PALB2* is a breast cancer susceptibility gene and its product was originally described to interact with BRCA2 via its C-terminal region. PALB2 also interacts with BRCA1 via its N-terminal region, playing a key role to form the BRCA1-PALB2-BRCA2 complex. This complex is crucial for homologous recombination and genomic stability. An increasing number of *PALB2* variants have been reported, but yet without proper classification for cancer association. As new therapies based on *PALB2* mutational status are being developed, the classification of variants acquire great importance. Our group have demonstrated a strong correlation between clinical and functional data involving the interaction of PALB2 and BRCA1 variants. **OBJECTIVES**: This project aims to establish a functional assay to evaluate PALB2 variants located at the N- and C-terminal domains by testing their ability to interact with BRCA1 and BRCA2, respectively. **MATERIALS AND METHODS:** The evaluation will be conducted by a mammalian two-hybrid approach using BRCA1 (aa 1314-1863) and BRCA2 (aa 1-60) as preys for PALB2-N-terminal and PALB2-C-terminal variants identified in the population. **RESULTS**: BRCA1, BRCA2 and PALB2 C- and N-terminal wild-type constructs were generated and pilot assay have already been performed. The functional assay for the PALB2-N-terminal region is already validated. Constructs coding for variants identified in the population are being generated, sequenced and protein fusions expression evaluated by immunoblotting. **CONCLUSION**: Several population-based and family-based studies have demonstrated that germline mutations in the *PALB2* gene are associated with an increased risk of breast cancer, also a growing number of *PALB2* variants are being identified in breast cancer patients. There is no functional evaluation method for PALB2 variants available. We believe that evaluating *PALB2* variants at their ability to maintain the BRCA1-PALB2-BRCA2 complex will help variants' classification, working as an important tool to predict their association to cancer. (*) Both authors contributed equally for this work.

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