Analysis of PALB2 Gene in Spanish Hereditary Breast Ovarian Cancer Families with Male Breast Cancer, without BRCA1 or BRCA2 Mutations

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on behalf of the Grupo Español para el estudio del gen PALB2 en familias BRCA1/2 negativas

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Inherited breast cancer with an autosomal dominant pattern of inheritance accounts for 5-10% of all breast cancer cases, and 20-25% of familial breast cancer is associated with mutations in BRCA1 and BRCA2. Other genes known to be linked to familial breast cancer, such as, CHEK2, ATM and FANCJ/BRIP1, participate in DNA damage responses, indicating that other genes in this pathway could also predispose to breast cancer. One of these genes is PALB2 (“Partner and Localizer of BRCA2”), which encodes a protein that functions in genome maintenance (double strand break repair). This protein binds to and co-localizes with the BRCA2 protein in nuclear foci and likely permits the stable intranuclear localization and accumulation of BRCA2.

Recently, PALB2 was considered as a moderate-penetrance breast cancer susceptibility gene, accounting for about 1% of BRCA1/2 negative familial and early onset breast cancers. PALB2 mutations were found in families with both female and male breast cancer cases, suggesting that PALB2 could be involved in male breast cancer risk. We aimed to evaluate the contribution of PALB2 mutations in 125 BRCA1/2 negative families with cases of male breast cancer collected from 13 centres throughout Spain. Direct sequencing of PALB2 gene and MLPA analysis is being performed.

Preliminary results showed 17 PALB2 variants: 3 in the 5‘UTR region, 4 intronic and 10 exonic. Four novel variants were identified. No truncating mutations were found. Four cases were carriers of a combination of PALB2 variants. Although these variants may be individually neutral, it cannot be excluded that a combination of variants may confer
susceptibility for breast cancer. The role that 5’UTR substitutions play in PALB2 regulation and breast cancer predisposition is currently unknown and will require further characterization of the promoter region of PALB2.

In our population PALB2 seems not to play a major role in HBOC families with male breast cancer. More studies are required to clarify the implication of rare PALB2 variants in breast cancer risk and to evaluate whether, following a polygenic model, the co-existence of multiple PALB2 variants may act as low-penetrant alleles.

Keywords: PALB2, germline mutations, male breast cancer.

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