In the Unit, we offer researchers access to state-of-the-art methods for high throughput genotyping and sequencing for a wide range of applications. We currently have available different genotyping and sequencing platforms to be used according to the scale of analysis required, and we are continuously developing new techniques to cover all research projects needs. The research carried out in the Unit is based on identifying genetic risk factors of breast cancer susceptibility and treatment response. Our main goals are to: i) improve individual breast cancer risk assessment, ii) develop novel strategies for breast cancer early detection, and iii) provide cancer patients more accurate and safe treatment.

**RESEARCH HIGHLIGHTS**

Breast cancer risks associated with missense variants in breast cancer susceptibility genes. This study is the result of the European project BRIDGES (Breast Cancer Risk after Diagnostic Gene Sequencing), in which the Unit participates. Protein truncating variants in ATM, BRCA1, BRCA2, CHEK2, and PALB2 are associated with increased breast cancer risk, but risks associated with missense variants in these genes are uncertain. We analysed 59,639 breast cancer cases and 53,165 controls for missense variants in these 5 breast cancer genes, evaluating the risk according to in silico prediction-of-deliberousness algorithms, functional protein domain, and frequency. For ATM, BRCA1, and BRCA2, data were compatible with small subsets (7%, 2%, and 0.6%, respectively) of rare missense variants giving similar risk to those of protein truncating variants in the same gene. For CHEK2, data were more consistent with a large fraction (approximately 60%) of rare missense variants giving a lower risk (OR 1.75, 95% CI (1.47-2.08)) than CHEK2 protein truncating variants. Our results could contribute to the clinical reporting of gene panel testing for breast cancer susceptibility (Dorling L et al. 2022).

Pathology of tumours associated with pathogenic germline variants in 9 breast cancer susceptibility genes. The main objective of this study was to determine the distribution of intrinsic subtypes in the 9 confirmed breast cancer genes — ATM, BARD1, BRCA1, BRCA2, CHEK2, PALB2, RAD51C, RAD51D, and TP53 — harbouring rare truncating variants and likely pathogenic missense variants associated with increased breast cancer risk. For this purpose, we used data from the BRIDGES project, including 42,680 patients recruited in Spain from 34 centres in 25 cities. The discovery stage of the study comprised up to 9,371 COVID-19 positive cases and 5,943 population controls. Replication was pursued in an additional 1,598 COVID-19 cases and 1,068 population controls, and in other studies from the Host Genetics Initiative. When we performed sex-disaggregated genome-wide association studies for COVID-19 hospitalisation, genome-wide significance (P < 5 × 10⁻⁸) was crossed for variants in 9p21.31 and 21q22.11 loci only among males (P = 1.3 × 10⁻¹⁰ and P = 8.1 × 10⁻⁹, respectively), and for variants in 9q21.32 near TLE1 only among females (P = 4.4 × 10⁻⁹). The results in the overall analysis revealed 2 novel risk loci in 9p21.3 and 19q13.12, associated with AQP3 (P = 2.7 × 10⁻⁸) and ARHGAAP32 (P = 1.3 × 10⁻⁸), respectively. In summary, new candidate variants for COVID-19 severity and evidence supporting genetic disparities among sexes are provided (Cruz R et al. 2022).

**PUBLICATIONS**

- Marchena-Pena Ehtafal (incl. Tejera-Perez H, Pita G, Najarro-Torre I) (2022). A large case-control study performed in Spanish population suggests that RECG3.5, the only RECG3 locus involved in breast cancer susceptibility. Cancers (Basel) 14, 4378.