Breast cancer risk genes - association analysis in more than 113,000 women. This study is the result of the European project BRIDGES (Breast Cancer Risk after Diagnostic Gene Sequencing), in which the Unit participates. The study was based on the analysis of 34 known or suspected breast cancer susceptibility genes in DNA samples from 66,400 women who had developed breast cancer and 53,400 healthy women. The results pinpoint 9 genes for which there is solid evidence of their involvement in the disease: ATM, BRCAl, BRC2, CHEK2, PALB2, BARDI, RAD51C, RAD51D and TP53. This was already known for some of these genes, but for others, such as RAD51C and D and BARDI, their involvement was not so well established. For all genes, more precise risk estimates can now be calculated, and these estimates are tailored for each tumour subtype. By contrast, the study shows that about 15 of the genes that have been used so far in some tests are not indicative of an increased risk for breast cancer and should therefore not be taken into account in risk estimates, at least at this time (Dorling L et al., 2021).

Characterisation of pharmacogenetic variability in the Spanish population. Pharmacogenomics (PGx) allows for patients to be managed in an individualised manner, leading to the better safety and efficacy of treatments. Nevertheless, genetic differences between populations need to be considered before implementing PGx. We used data from 30066 Spanish individuals to analyse pharmacogenetic variation in the most important pharmacogenes for population characterisation. For 21 clinically relevant pharmacogenes, our analysis revealed that 98% of the Spanish individuals harbour at least 1 allele that leads to a change in the therapy. We also identified 7775 putative pathogenic SNVs and 33 CNVs. This study provided useful information to facilitate PGx implementation in our country by (i) confirming that almost all Spanish individuals could benefit from pharmacogenetics diagnostics; (ii) identifying additional pathogenic pharmacovariants with a possible functional role, data freely available to the public by accessing the Collaborative Spanish Variant Server; and (iii) demonstrating that PGx microarrays can be a cost-effective solution for testing.

POLTAM as a novel susceptibility gene for cardio toxicity in epirubicin treatment of breast cancer patients. Anthracyclines are among the most used chemotherapeutic agents in breast cancer (BC). However, their use is hampered by anthracycline-induced cardiotoxicity (AIC). To identify novel predictive genes, we conducted a 2-stage genome-wide association study in epirubicin-treated BC patients. The most interesting and replicated finding was rs62134260, located 4kb upstream of POLRTAM (OR = 5.76, P = 2.23 × 10−3). This variant regulates the expression of POLRTAM, a gene that encodes a mitochondrial DNA-directed RNA polymerase, responsible for mitochondrial gene expression. Individuals harbouring the risk allele had decreased expression of POLRTAM in heart tissue, which may cause impaired capacity to maintain a healthy mitochondrial population in cardiomyocytes under stress conditions, such as is the case with epirubicin treatment. This finding suggests a novel molecular mechanism involved in the development of AIC and may improve our ability to predict which patients are at risk (Velasco-Ruíz A et al., 2021).

“Our goal is to identify predictive markers in cancer that allow individual risk assessment, thus integrating personalised medicine into healthcare practice.”

**OVERVIEW**

In the Unit we implement high-throughput and cost-effective methods to measure from one to millions of genetic variants, mainly single nucleotide variants (SNVs) and copy number variants (CNVs). Epigenetic analyses are also performed. Complementarily, our research focuses on identifying genes associated with cancer risk and response to therapy to understand the underlying molecular mechanisms of cancer susceptibility and drug efficacy/toxicity and to improve individual risk assessment for the identification of high-risk populations.

**PUBLICATIONS**