The Human Genetics Group is working on the study of human cancer from a genetic, cytogenetic and epidemiologic point of view. We want to understand why the inherited susceptibility to cancer doesn’t follow a mathematical model in people, but rather ‘an apparently random model’, and why there are families with a large number of members suffering from cancer.

For these studies we work with individuals, families and the affected and normal population, trying to perform a correct diagnosis with known genes as well as looking for new genes that could explain cancer susceptibility in specific families. Our main objective is to work with every family by raising their awareness in regards to their own risk of developing cancer and how to prevent it. To this primary level, we have to add a secondary level of prevention, which will facilitate an important risk reduction in the population, through the development of non-invasive and non-genetic but yet extremely effective measures.

“During 2016, we showed how inhibitors, other than PARPi, could be used in patients with BRCA mutations. We started working on the identification of new treatments for cardiac tumours based on transcriptome analysis, and finally, we are also exploring a polygenic inheritance model in families with testicular cancer that is based on more than 25 identified genes associated with this disease.”

**Breast cancer: PARPi and OGG1 inhibitors in BRCA1 mutation carriers**

We have demonstrated that certain missense mutations in BRCA1 seem to make cells more sensitive to Poly (ADP-ribose) Polymerase (PARP) inhibitors than those mutations that give rise to the absence of the protein (frameshift mutations) (T. Valclová, Hum Mol Genet 2016). We are currently investigating the mechanisms underlying these differences with the aim of identifying new markers of sensitivity or resistance to these agents.

In parallel, we recently showed that the Single Nucleotide Polymorphism (SNP) rs2304277 located in the 3’ untranslated region (UTR) of the OGG1 DNA glycosylase gene of the Base Excision Repair pathway (BER), modified cancer risk in patients harbouring mutations in BRCA1 (Osorio A. et al., Plos Genetics, 2014). We have identified that the SNP is associated with a constitutive HOGG1 transcriptional downregulation, which leads to a high genome and telomere instability in those patients harbouring BRCA1 and BRCA2 mutations, thereby explaining the contribution of this polymorphism to cancer risk. This association is most likely explained by a synthetic lethal/sick interaction between these 2 genetic events (Benitez-Buelga C. et al., Oncotarget, 2016). In order to take an in-depth look at the biological link between BER and the homologous recombination (HR) DNA repair pathway, we tested the pharmacological inhibition of OGG1 in a set of BRCA1 and BRCA2 deficient cancer cell lines. We found that OGG1 inhibition is effective, leading to 1) an accumulation of telomere oxidation (genomic instability), and 2) an alteration in the normal proliferation of BRCA1 deficient cell lines, pointing to a synthetic lethal interaction between OGG1 and BRCA1 (FIGURE 1).

**Familial cancer exome project**

This project started several years ago with the objective of identifying new high susceptibility genes that explain families...
with rare tumours as well as deciphering the genetic heterogeneity present in some of them.

In 2015, we identified ATM as being responsible for families with gastric neuroendocrine tumours. We are currently searching for new genes in cancer families that cannot be explained by mutations in ATM.

A second gene, POT, which was published in 2015 as being associated with familial cardiac angiosarcoma, also explains some families with Li Fraumeni-like syndrome. Analysis of tumour samples with Next Generation Sequencing (NGS) has shown an over-representation of the anigioendothelial, pathway, which is useful in clinical collaborations. In collaboration with M. Blasco’s Telemerase and Telomerase Group, we are generating a knock-in mouse with the aim of recapitulating the disease, as well as enabling us to work with antiangiogenic drugs.

We are currently investigating a large family with meningiomas across 3 generations. Analysis of the data generated using bioinformatics tools has shown the existence of 2 candidate genes that could be responsible for this family. We are starting functional studies and are recruiting more families.

Ovarian cancer families are rare and are usually associated with breast cancer. We sequenced the exomes of 9 patients from 5 families and identified 38 rare variants in 28 genes potentially implicated in ovarian cancer risk. By conducting a case-control association study we narrowed down the number of candidate missense variants to 10. These, together with high-impact variants (protein truncating or splicing variants), will be evaluated in a larger international case control study to finally define their role in ovarian cancer susceptibility. In parallel, we selected a non-described RAD50C missense variant among the identified candidate, and through functional characterisation we were able to determine its pathogenicity and its probable involvement in ovarian cancer risk in one of the families. This finding not only has implications for genetic counselling but also for the potential treatment of affected carriers with PARPi.

Breast cancer. We have performed whole-exome sequencing (WES) in 3 BRCAX families (familial breast cancer families negative for mutations in BRCA1/3). One of the families was found to harbour a deleterious mutation in the known breast cancer susceptibility gene ATM. A complete screening of this gene in a set of 400 Spanish breast cancer families showed a prevalence of almost 2% of mutations in ATM, higher than that reported in other populations (Taveras-Tapia et al., BCRIT 2016). In another family, we found an excellent candidate breast cancer gene that is currently being screened by targeted NGS in a series of 700 BRCAX families and 700 controls. The third family is still under analysis.

Male breast cancer. We performed WES in a male breast cancer family with an apparently recessive model of inheritance. We have found 7 candidate variants that are currently being validated in a series of 1000 male breast cancer cases and 1000 controls; this is undertaken in collaboration with Nick Orr’s lab at the Institute of Cancer Research in London.

**AFFECTED INDIVIDUALS vs HEALTHY CONTROLS**

![Image](https://via.placeholder.com/150)

**Figure 1** Different strategies used in the polygenic analysis of families with testicular cancer.

**AFFECTED INDIVIDUALS vs CONTROLS**

![Image](https://via.placeholder.com/150)

**Figure 2** Differenct strategies used in the polygenic analysis of families with testicular cancer.