# FAMILIAL CANCER CLINICAL UNIT

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## OVERVIEW

The Unit's activity is divided into 2 main areas:

1. *Genetic diagnosis of cancer patients, especially those at a young age, with multiple tumours or other family members with cancer.* Elucidating hereditary cancer helps the physician to decide on appropriate treatment and, for risk relatives, to initiate preventive strategies if they are carriers. We work mainly with colorectal cancer/Lynch syndrome and breast/ovarian cancer, but we are also a referral unit for rare genetic-based and cancer-related diseases. We provide genetic diagnosis at the Familial Cancer Consultancy (FCC) of the University Hospital of Fuenlabrada (UHF), but also in other hospitals in Madrid and the rest of Spain.
2. *Research work on the elucidation of genetic factors related to familial breast and colorectal cancer*. We focus on identifying new driver genes and clarifying their role in patient management. In addition, we are interested in genetic risk factors, prognostic markers, and genetic and molecular factors that could affect therapeutics.

**"The Familial Cancer Clinical Unit (FCCU) has confirmed *RECQL5* as a novel breast cancer gene and has been involved in understanding the role of OGG1, *BRCA* carrier modifiers, and the first germline biallelic mutation in *MAD1L1*."**





Technicians
Alicia Barroso (until September), Victoria Fernández (TS)*, Verónica García (TS)*, Maika González-Neira, Fátima Mercadillo

*Titulado Superior* (Advanced Degree)

Master´s Student
Milton Eduardo Salazar (Jan.-Sep.) (*Universidad Complutense de Madrid*, Spain)

## RESEARCH HIGHLIGHTS

**Clinical and diagnostic activity.** The catalogue of genes has been updated and expanded to tumours that were not previously covered. 729 patients visited our consultancy at the UHF, and 1884 genetic studies were carried out in the FCCU laboratory.

**Elucidating new breast cancer (BC) genes.** We found a statistically significant association between loss-of-function variants in the *RECQL5* gene and BC risk in almost 2000 index cases of Spanish BC families, supporting its role as a novel moderate-risk BC gene.

**Understanding the role of new variants in moderate-risk BC genes.** Through a mutational analysis of the *BARD1* gene, in a cohort of 1946 Spanish patients with BC using NGS, we saw that the prevalence and spectrum of *BARD1* mutations could vary between different regions of Spain and highlighted the relevance of analysing copy number variations.

**New BC therapeutic approaches.** Osorio was involved in the discovery that TH5487, an inhibitor of 8-oxoguanine DNA glycosylase 1 (OGG1), increases sensitivity to the PARP inhibitor Olaparib, especially in the context of BRCA1 deficiency. She was also involved in the description of TH10785, which increases OGG1 recruitment and repair of oxidative DNA damage that may have therapeutic applications.

**Contributions to the diagnosis and clinical follow-up of PTEN hamartoma tumour syndrome (PHTS).** In the largest study performed in the Spanish population with clinical features of PHTS (n = 145), we concluded that to improve clinical diagnosis we should focus on macrocephaly, mucocutaneous lesions, obesity, and gastrointestinal polyposis. We pointed out the importance of regular weight control and of considering cancer screening at an earlier age. In addition, we participated in an extensive functional characterisation of variants of unknown significance identified in patients with PHTS.

**Mosaic variegated aneuploidy (MVA).** Urioste was involved in the description of the first germline biallelic mutation in *MAD1L1* as a novel cause of aneuploidy in an individual with no intellectual disability and an unprecedented number of neoplasias, including 5 malignant tumours before the age of 36. ■

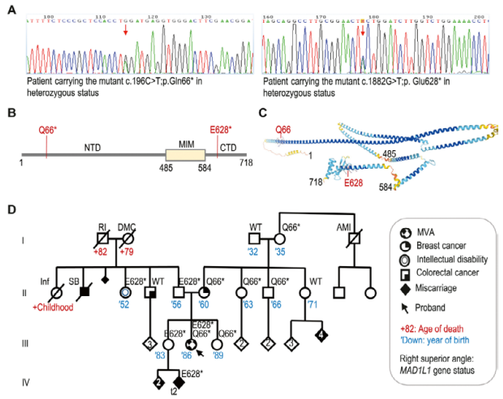


**FIGURE 1** Biallelic loss-of-function mutations in *MAD1L1*. (**A**) *MAD1L1* mutations in the proband. (**B**) Schematic representation of the MAD1 protein and the mutations found in the proband. NTD, N-terminal domain; MIM, MAD2 interaction motif. (**C**) Predicted structure of MAD1 and the position of the Q66 and E628 mutated residues. (**D**) Pedigree of the family. AMI, acute myocardial infarction; DMC, diabetes mellitus complications; Inf, infection; RI, renal insufficiency; SB, stillbirth; t2, trisomy chromosome 2.

### SELECTED PUBLICATIONS


- Michel M *et al.* (incl. Osorio A) (2022). Small-molecule activation of OGG1 increases oxidative DNA damage repair by gaining a new function. *Science* 376, 1471-1476.
- Breast Cancer Association Consortium *et al.* (incl. Osorio A) (2022). Pathology of tumors associated with pathogenic germline variants in 9 breast cancer susceptibility genes. *JAMA Oncol* 8, e216744.
- Villarroya-Beltri C *et al.* (incl. Osorio A, Mercadillo F, Urioste M) (2022). Biallelic germline mutations in MAD1L1 induce a syndrome of aneuploidy with hightumor susceptibility. *Sci Adv* 8, eabq5914.
- Marchena-Perea EM *et al.* (incl. Currás-Freixes M, Osorio A) (2022). A large case-control study performed in Spanish population suggests that RECQL5 is the only RECQ helicase involved in breast cancer susceptibility. *Cancers (Basel)* 14, 4738.
- Torices L *et al.* (incl. Mercadillo F, Currás M, Urioste M) (2022). Functional analysis of PTEN variants of unknown significance from PHTS patients unveils complex patterns of PTEN biological activity in disease. *Eur J Hum Genet*. PMID: 36543932.
- Grootes I *et al.* (incl. Osorio A) (2022). Incorporating progesterone receptor expression into the PREDICT breast prognostic model. *Eur J Cancer* 173, 178-193.
- Baquero JM *et al.* (incl. Osorio A) (2022). OGG1 inhibition triggers synthetic lethality and enhances the effect of PARP inhibitor olaparib in BRCA1-deficient TNBC cells. *Front Oncol* 12, 888810.