

FAMILIAL CANCER CLINICAL UNIT

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OVERVIEW

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

1. *Genetic diagnosis in patients with suspected hereditary cancer using next-generation sequencing.* 52% of our activity is dedicated to genetic diagnosis in the Familial Cancer Clinic of the University Hospital of Fuenlabrada (FCC-UHF), and 48% to providing this service to other hospitals in Madrid and the rest of Spain. 59% of the genetic diagnoses were carried out in index cases, while 41% were predictive studies in relatives to determine if they are carriers of a variant. We completed 203 urgent case studies to guide surgery and/or treatment, with results reported in less than 6-8 weeks. We also performed up to 50 extensions of previous studies (gene updates/tumour) and 67 variant reclassification reports (genetic information updates).

“The FCCU performed genetic diagnoses on more than 2000 patients, and more than 1000 were evaluated at the FCC-UHF. We played an important role in selecting families for the execution of the IMPaCT-GENÓMICA project.”

2. *Research work.* We participated in the identification of genetic factors and the interpretation of genetic variants of unknown significance (VUS) in the PTEN Hamartoma Tumour Syndrome (PHTS). We are involved in the IMPaCT-GENÓMICA and IMPACT-VUScan projects, having been one of the main participants in the Spanish Hereditary Cancer Variants Database (SpadaHC).

RESEARCH HIGHLIGHTS

Clinical and diagnostic activity

1068 patients were evaluated at the FCC-UHF and 2016 genetic studies were performed at the Familial Cancer Clinical Unit (FCCU) during 2023. A total of 355 pathogenic or probable pathogenic variants were identified, allowing families and patients to benefit from appropriate clinical follow-up, early detection in unaffected patients, and/or personalised medicine. We implemented the diagnosis of MLH1 methylation in endometrial and colorectal tumours and the genetic diagnosis of healthy individuals with deceased relatives affected by cancer. In addition, we updated the genes to be studied per tumour and expanded the range of tumours in which the presence of germline mutations is excluded (including bladder and genitourinary tract tumours, among others).

IMPaCT-GENÓMICA

This project aims to identify genetic variants that could explain cancer predisposition. The FCCU participated, among other centres in Spain, in the clinical decision-making committee to choose the most appropriate unsolved familial cases. A total of 22 families from Madrid and 169 Spanish families were recruited. Our Unit contributed 6 families with cases related to prostate (3), testicular (1), pancreatic (1), and breast (1) cancers.

We will also be involved in the analysis and integration of data for candidate variant prioritisation and functional evaluation, among other CNIO Groups and Units.

SpadaHC

SpadaHC is a database for sharing genetic variants identified in hereditary cancer genes, which currently includes data from 15 Spanish genetic diagnostic reference laboratories. The database also provides frequencies of these variants in the Spanish population and is a useful resource for research and clinical genetic laboratories to improve knowledge of the genetic basis of hereditary cancer.

The current version of the database contains 1.16M genetic variants from 4294 individuals and 14776 variant classifications. A total of 2469 variants had different pathogenicity classifications, and we participated in their homogenisation. For this purpose, we took into account the criteria of the American College of Medical Genetics and the results of our laboratory, and resolved the discrepancies in 84 clinically relevant variants. For most of the variants, a consensus on the best classification was reached to provide better clinical decision-making support.

PTEN variants

We participated in the comprehensive functional characterisation of 6 novel variants of unknown significance identified in the *PTEN* gene and also initiated a collaboration with the PTEN Research Foundation on premalignant lesions and vascular malformations in patients with PHTS. ■

PUBLICATIONS

- Pairo-Castineira E *et al.* (incl. Mercadillo F as collaborator) (2023). GWAS and meta-analysis identifies 49 genetic variants underlying critical COVID-19. *Nature* 617, 764-768.
- Calsina B *et al.* (incl. Currás-Freixes M, Gil E) (2023). Genomic and immune landscape of metastatic pheochromocytoma and paraganglioma. *Nat Commun* 14, 1122.
- Mellid S *et al.* (incl. Calsina B, Gil E) (2023). DLST mutations in pheochromocytoma

- and paraganglioma cause proteome hypsuccinylation and metabolic remodeling. *Cancer Commun (Lond)* 43, 838-843.
- Castro-Santos P *et al.* (incl. Mercadillo F as collaborator) (2023). HLA-A*11:01 and HLA-C*04:01 are associated with severe COVID-19. *HLA* 102, 731-739.
- Roldán-Romero JM *et al.* (incl. Calsina B) (2023). Deubiquitinase USP9X loss sensitizes renal cancer cells to mTOR inhibition. *Int J Cancer* 153, 1300-1312.
- Mellid S *et al.* (incl. Gil E) (2023) Co-occurrence of mutations in NF1 and other suscep-

- tibility genes in pheochromocytoma and paraganglioma. *Front Endocrinol (Lausanne)* 13, 1070074.
- Torices L *et al.* (incl. Mercadillo F, Currás M). (2023). Functional analysis of PTEN variants of unknown significance from PHTS patients unveils complex patterns of PTEN biological activity in disease. *Eur J Hum Genet* 31, 568-577.
- Cascón A *et al.* (incl. Calsina B, Currás-Freixes M) (2023). Genetic bases of pheochromocytoma and paraganglioma. *J Mol Endocrinol* 70, e220167.

- Li M *et al.* (incl. Calsina B) (2023). Regulation of epinephrine biosynthesis in HRAS-mutant paragangliomas. *Endocr Relat Cancer* 30, e230230.

AWARDS AND RECOGNITION

- Bruna Calsina :
- ENSAT Scientific Award, The European Network for the Study of Adrenal Tumors (ENSAT).
- Award for PhD-Authored Publications, CNIO Lab day.