

Genetic and Molecular Epidemiology Group

Summary

The scope of the Cancer Epidemiology Group ranges from aetiology to clinical and Public Health importance, focusing on three diseases: bladder, pancreatic, and breast cancer. Epidemiology is now in an era that demands the alignment and synergy of scope, objectives, data, and tools across disciplines. By applying an integrative research approach, we participate in large, international and multidisciplinary studies requiring the development of methodological innovations in all aspects of epidemiology. We employ a wide variety of biomarkers to better characterise exposure and cancer outcomes, as well as the genetic patterns predisposing or protecting against the disease, including variability in its clinical course.

Strategic Goals

- Identify genetic susceptibility factors and gene* environmental interactions involved in cancer and assess their role in cancer progression
- Characterise tumour subphenotypes by applying pathological and molecular markers and study their differential association with germline genetic variants and environmental risk exposure
- Develop statistical/informatics tools to integrate epidemiologic, genetic, genomic and clinical data, and to model the clinical course of patients with cancer
- Assess public health strategies for cancer control using current advances in genetics and their usefulness in clinical practices

Núria Malats *Group Leader*



Núria Malats was born in 1962 in Barcelona, Spain. She obtained her MD in 1986 and her PhD in 1995 from the *Universitat Autònoma de Barcelona* and was one of the first scientists working in genetic and molecular epidemiology in Spain.

From 1992-1995 she coordinated a national multicentre project on the molecular epidemiology of pancreatic cancer (PANKRAS2). In 1996 she was Visiting Scientist at the International Agency for Research on Cancer (IARC-WHO) in Lyon, France, where she trained until 1998 in genetic epidemiology. She then returned to Spain in 1998 and obtained a research contract from the Ministry of Health.

Prior to joining the CNIO in September 2007 she was a Scientist at the *Centre de Recerca en Epidemiologia Ambiental* (CREAL-IMIM, Barcelona), leading and participating in national and international competitively funded projects, and she also coordinated the Spanish research network on bladder cancer.

She is PI of the European Study on Pancreatic Cancer Genetics and Epidemiology (PanGen-EU) and co-PI of the Spanish Bladder Cancer/EPICURO Study which is a large case-control/cohort study integrating scientific interests from different disciplines in bladder cancer development and progression.

Malats is the Spanish delegate of the Public Health Genomics European Network (PHGEN) and has participated in teaching programmes for under- and post-graduate courses at several universities. She is Member of the Scientific Board of the European Society of Urological Research (ESUR) and the European Association of Urology Research Foundation.



Post-doctoral fellows: Evelina Mocchi, André F. Santos. **Graduate students:** Maciej J. Czachorowski, Gaëlle Marenne, Antonio C. Picornell. **Technicians:** Ana Alfaro, Gabriela J. Andres, Gema Carretero (until October), Patricia González, Carlos Gonzalez (since September), Esther López (since April), Ángel López (until April, Collaborator until June), Esther Manso (since April), Mirari Márquez (since April), Giovanna M. Mauricio (until October), Roger L. Milne, Janire Rodríguez (since July).

Highlights

Bladder cancer

Spain has the highest incidence rates of urothelium carcinoma among men. This complex disease model is a good example of the role low penetrance genes and gene*environmental interactions play in carcinogenesis.

The Spanish Bladder Cancer / EPICURO Study is a collaboration between the CNIO; the *Centre de Recerca en Epidemiologia Ambiental- Institut Municipal d'Investigació Mèdica CREAL-IMIM*, Barcelona; and the National Cancer Institute – National Institutes of Health (NCI-NIH), USA. This study aims at integrating a large amount of information on genetic susceptibility factors, environmental exposure and lifestyle factors, as well as somatic genetic alterations in tumour tissue, clinical and pathological characteristics, and patient outcomes. To achieve this, the study recruited 1,356 cases and 1,271 controls from 18 Spanish hospitals from 1997 – 2001.

The study has involved high throughput genotyping and statistical approaches including a 1M probe Infinium-Illumina genome wide association/prognostic study (GWAS/GWPS) with both SNPs and Copy Number Variation (CNV). A significant number of identified signals (p -value $< 10^{-6}$) across the genome are now being replicated by independent groups and validated in the lab. We have observed a highly significant increased risk of bladder cancer associated

with certain types of mosaicisms.

A preliminary analysis using a tagSNP-candidate-pathway approach identified the selenoprotein, telomerase, and FGFR3 pathways as candidates for further exploration. In this regard, a recently published study has suggested a differential association between a large set of SNPs and distinct pathologically defined bladder cancer subphenotypes.

The Group is carrying out a wide, cross-cancer and integrative project aimed at assessing the association of the chronic inflammatory response and oxidative stress with cancer development and progression. Analyses of inflammation markers in tissue microarrays are being conducted. The interests of the Group surround environmental exposure, focusing on metals, organochlorine pesticides, and inflammatory-related conditions.

We are conducting a large ongoing joint effort involving the CNIO, *Universitat de Vic*, Barcelona, and *Fondation Jean Dausset / CEPH*, Paris, to innovate and apply novel analytical strategies facilitating disease modelling to better understand both the molecular pathophysiology and clinical course of bladder cancer patients.



Figure 1: Centres and countries participating in the European Study on Chronic Pancreas Diseases and Genetics (PanGen-EU Study): Spain: *Centro Nacional de Investigación Oncológicas*, Madrid, *Institut Municipal d'Investigació Mèdica*, Barcelona, *Hospital del Mar*, Barcelona, *Hospital de Sant Pau*, Barcelona, *Hospital Vall d'Hebron*, Barcelona, *Hospital Universitario de Oviedo*, *Hospital Clínico de Salamanca*, *Hospital Universitario de Santiago de Compostela*, *Hospital Universitario de Elche*, *Hospital 12 de Octubre*, Madrid, *Hospital Ramón y Cajal*, Madrid, *Hospital Oncológico Integral "Clara Campal"*, Madrid; Germany: *Philipps-Universität Marburg*, *Technische Universität München*; UK: University of Liverpool, Queen Mary University of London; Italy: *Università di Verona*; Sweden: Karolinska Institute, Stockholm; Ireland: the centres participating in the PanCAM Study.

We are involved in the Integrated Study on Bladder Cancer (ISBlC study) that is composed by three EU-funded projects (DropTop <http://www.drop-top.net/>, UROMOL <http://uromol.eu/index.php>, and DECanBIO <http://www.decanbio.eu>) aimed at identifying and validating prognostic and predictive markers for non-muscle invasive bladder cancer. A nomogram simultaneously integrating data from protein, SNP, and transcript markers with a predictive power will ultimately be developed.

Pancreatic cancer

Germline genetic factors play a critical role in the development of pancreatic cancer and better control of this disease would not be possible without a much deeper understanding of the inherited and environmental factors involved in progression of this cancer.

We have designed and coordinated a 2000 case – 2000 control study (*PanGen-EU*) within the MOLDIAG-PACA Integrated Project (<http://www.moldiagpaca.eu/>), which is being carried out in 28 hospitals throughout 7 EU countries. This study aims at identifying gene-environmental interactions associated with pancreatic cancer risk.

Breast cancer

By integrating our interests with those of the CNIO Human Genetics Group, we focus on the exploration of G*E interactions associated with breast cancer as well as the assessment of disease heterogeneity at the etiological level in relation to breast cancer subphenotypes. From January – April 2009 our Group hosted D. Goldgar, an internationally renowned genetic statistician, which led to several collaborations.

In addition to a large multicentre case-control study (*MamaGen*), we are actively collaborating in several studies within International Consortia; some of which have resulted in our identification of the differential association of the 2q35-rs13387042 with breast cancer subphenotypes. Furthermore, we are responsible for the statistical modelling of G*E interactions of 12 SNPs associated with breast cancer in 60,000 individuals.

Public Health and Genomics (PHGEN)

We participate in the European Network of Excellence in Genomics and Public Health (PHGEN) (<http://www.phgen.nrw.de>) assessing the implications of using genetic data in populations (genetic testing, biobanks, and legal issues).

Our Group is partially funded by the *Fondo de Investigación Sanitaria–Instituto de Salud Carlos III*, *Ministerio de Ciencia e Innovación*, and *Fundació Marató TV3*, Spain; AICR and EU-6th and 7th Framework Programme, Europe; and National Cancer Institute Intramural Funds and National Institutes of Health-RO1 Grant, USA.

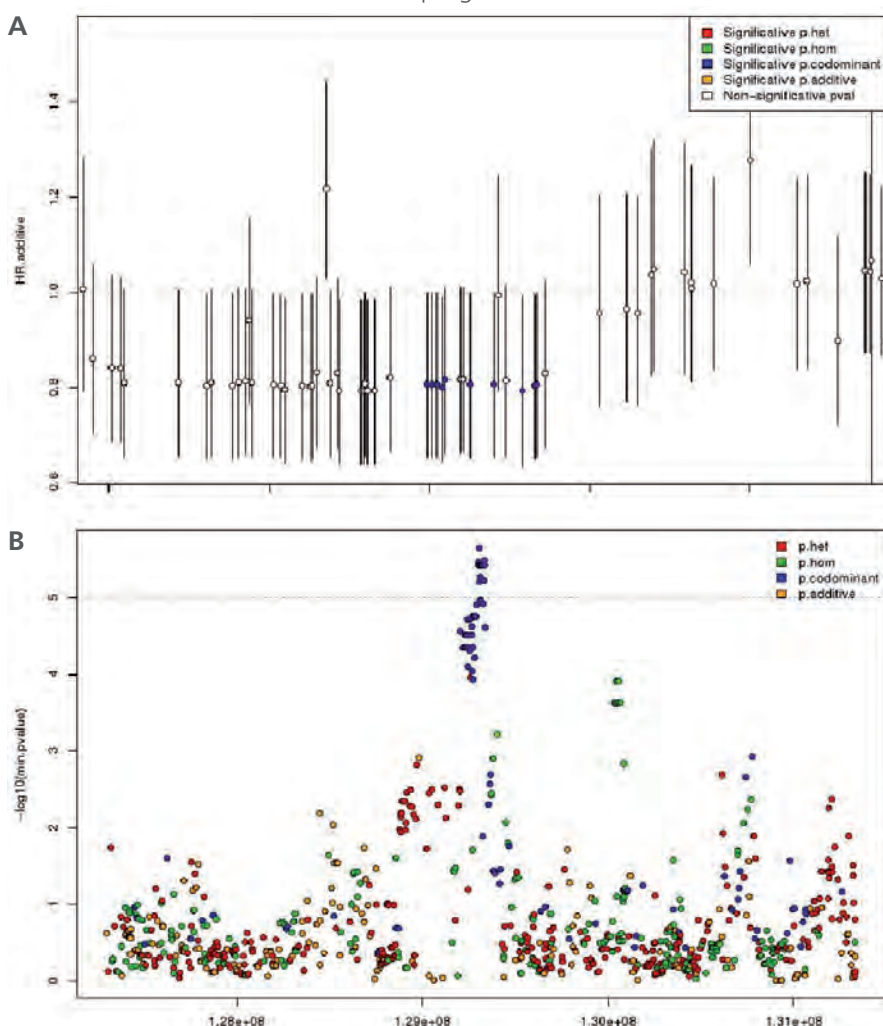


Figure 2: Genome Wide Prognostic Study (GWPS) in bladder cancer: Hazard ratios and confidence intervals (A) and log p values (B) for the SNPs included in a genomic cytoband that provided significant results.

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Awards and Recognition

Survey expert on best practice in prognosis research, *British Medical Journal* and the Royal Society of Medicine, UK