

# Genetic and Molecular Epidemiology Group



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 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 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, both being large case-control/cohort studies integrating scientific interests from different disciplines in 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.

## Summary

The scope of research carried out by the Cancer Epidemiology Group ranges from the identification of aetiological mechanisms to the translation of the research findings into clinical and Public Health domains, focusing on 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 adopting 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 environmental exposures, genetic susceptibility factors and gene\*environmental interactions involved in cancer development and progression
- Study the differential association of germline genetic variants and environmental exposure with cancer subphenotypes characterised at the molecular level
- Develop statistical/informatic tools to model the clinical course of patients with cancer and to integrate epidemiologic, (epi)genetic, genomics, and clinical data
- Assess clinical and public health strategies for cancer control using current genomic tests and data



**Post-doctoral fellows:** Evelina Mocci, André F. Santos and M. Evangelina López de Maturana (since May). **Graduate students:** Maciej J. Czachorowski, Gaëlle Marenne, Antonio C. Picornell and Salman M. Tajuddin (since May). **Technicians:** Ana Alfaro, Gabriela Andres, Carlos González, Jesús Herranz (since April), Esther López, Esther Manso, Mirari Márquez, Roger L. Milne and Janire Rodríguez.

## Highlights

### Bladder cancer

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

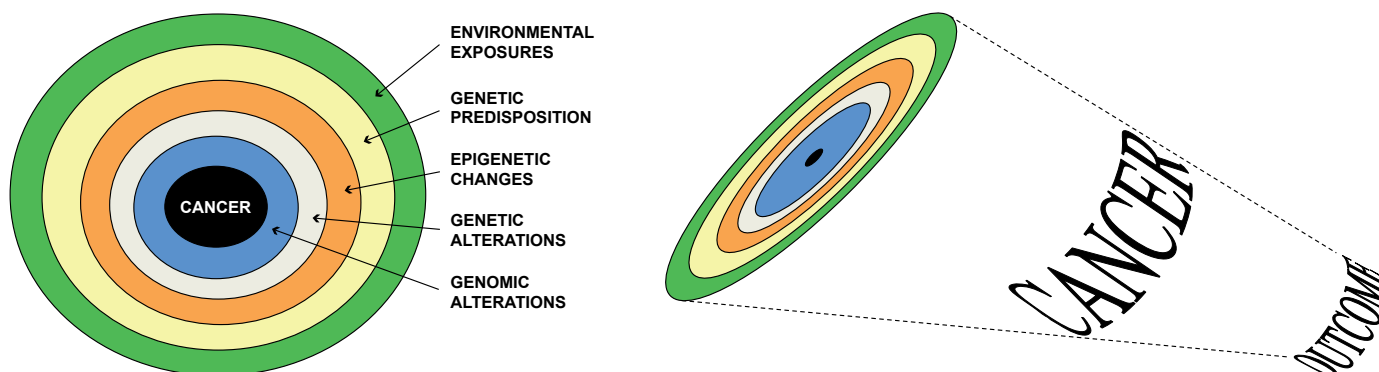
The Group applies a multilayered integrative approach (Figure 1) by combining data from the Spanish Bladder Cancer (SBC) / EPICURO Study and the Integrated Study on Bladder Cancer (ISBlac). The SBC/EPICURO Study is a collaboration between the CNIO, the *Centre de Recerca en Epidemiologia Ambiental-Institut Municipal d'Investigació Mèdica* (CREAL-IMIM), Barcelona, and the National Cancer Institute – National Institutes of Health (NCI-NIH), USA. This study has recruited 1,356 cases and 1,271 controls

from 18 Spanish hospitals from 1997-2001 and collected detailed information from these patients obtained from the different layers displayed in Figure 1.

The ISBlac study is composed of three EU-funded projects (DropTop, UROMOL, and DECanBIO) and aims to develop a prognostic algorithm by simultaneously integrating data from protein, SNP, candidate gene mutations, and transcript markers. A new on-going European study will serve to validate the markers and the predictive algorithm.

We are particularly interested in inherited genetic susceptibility in relation to bladder cancer risk and prognosis. To this end, our Group leads and participates in high-throughput genotyping and statistical approaches, including a 1M probe Infinium-Illumina genome wide association/prognostic study (GWAS/GWPS) with both

### MULTILAYERED APPROACH and... TIME



**Figure 1:** Multilayered approach to cancer research. Cancer results from the zoom effect of the interaction among several types of factors. The zoom can be viewed as multilayered mechanisms with the environmental exposures located in the outside layer. Interactions between layers and their effects on the disease change through time.

SNPs and Copy Number Variation (CNV). A significant number of identified signals across the genome are now being replicated and validated by independent groups and in the lab, respectively.

Analyses using a tagSNP-candidate-pathway approach identified candidate pathways and genes that are now being further explored. A study published by our Group has suggested a differential association between a large set of SNPs and distinct pathologically defined bladder cancer subphenotypes. We have undertaken a similar approach by applying molecular definitions to bladder cancer subtypes. Furthermore, we have observed a highly significant increased risk of bladder cancer associated with certain types of mosaicisms.

Our group is also 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 and oxidative stress markers in tissue microarrays are being conducted. The interests of the Group surround environmental exposure, focusing on metals and inflammatory-related conditions.

We have also undertaken another study in collaboration with the *Instituto Universitario de Oncología del Principado de Asturias* (IUOPA) – a global assessment of hypomethylation with bladder cancer risk considering both epidemiological and genetic data. Furthermore, initial attempts are currently ongoing to integrate GWAS and gene expression data.

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

## Pancreatic cancer

Inflammation and germline genetic factors play a critical role in the development of pancreatic cancer. Better control of

this disease will not be possible without a much deeper understanding of the inherited and environmental factors involved in progression of this cancer. To this end, we have genotyped cases from two retrospective studies (PANKRAS2 and the Ontario Pancreas Cancer Study) and assessed the association between SNPs involved in the inflammatory response and bladder cancer risk.

We have designed and coordinated a large ongoing European case-control study (*PanGen-EU*), which is being carried out throughout 28 centres in 7 countries (Figure 2). The large size, the standardised methodology applied in all participant centres, the detailed epidemiological and clinical information being collected and the biological samples obtained, place this study in a unique position in the post-GWAS era. This study both validates previous findings and further explores the development and progression mechanisms of this aggressive disease by applying epidemiological methods and data obtained from the multiple layers depicted in Figure 1.

## 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



**Figure 2:** Centres and countries participating in the European Study on Chronic Pancreas Diseases and Genetics (*PanGen-EU* Study): Spain: *Centro Nacional de Investigaciones 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.

etiological level in relation to breast cancer subphenotypes.

We are actively collaborating in several studies within International Consortia, some of which have resulted in the identification and replication of genetic variants in both sporadic and familial breast cancer patients. 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 II) assessing the implications of

using genomic data and technology 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* (MICINN), *Fundación "la Caixa"*, *Fundación Banco de Santander*, Spain; AICR, WCRF, and 7<sup>th</sup> Framework Programmes, Europe; and National Cancer Institute Intramural Funds and National Institutes of Health-RO1 Grant, USA.

## Publications

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