

# Human Genotyping-CEGEN Core Unit



Anna González-Neira

## Unit Head

Anna González-Neira was born in London in 1971 and studied at the *Universidad Complutense de Madrid* where she graduated in Biology in 1995. In 1996 she joined the Faculty of Medicine, the *Universidad de Santiago de Compostela* (Spain), where she obtained her PhD degree in Medicine under the supervision of A. Carracedo for which she was awarded the Thesis Prize.

During this period she was also a Research Fellow at the Office of the Chief Medical Examiner, Department of Forensic Biology, New York University Medical Centre (USA) and at the Institute of Pathology and Molecular Immunology (IPATIMUP), *Universidade do Porto*, Portugal.

She spent three years as a Postdoctoral Fellow at the Unit of Evolutionary Biology, *Universidad Pompeu Fabra* in Barcelona under the supervision of J. Bertranpetit. She has also held fellowships at the *Wellcome Trust Sanger Institute*, Cambridge (UK) in the groups of I. Dunham and P. Deloukas and later moved to Oxford (UK) to work at the Department of Bioinformatics and Statistical Genetics, Wellcome Centre of Human Genetics, supervised by L. Cardon.

Anna joined the CNIO in September 2004 to head the Human Genotyping Core Unit.

Her current research focuses on the identification of genetic factors associated with efficacy and toxicity of anticancer drugs.

## Summary

The most abundant types of genetic variations are single nucleotide polymorphisms (SNPs), however, structural variation changes including copy number variants (CNVs) are proving more common than expected. Both types of variants play an important role in the inter-individual differences observed in relation to disease susceptibility and response to drug therapy.

The advancement of high-throughput and cost-effective methods to measure genetic variation in thousands as well as millions of variants is allowing researchers to perform this analysis at a genome-wide level. This new approach offers a more comprehensive analysis of genetic factors associated with cancer risk and drug efficacy.

## Main Objectives

- Establish and validate new high-throughput methods to measure genetic variation
- Provide bioinformatics support for data management, data analysis, and interpretation of results
- Identify genetic factors influencing the efficacy and toxicity of anticancer drugs





**Graduate students:** Daniela Caronia and Sara Ruiz (since September). **Technicians:** M. Rosario Alonso, Nuria Álvarez, Belén Herráez, Daniel Herrero (since July), María Lacruz (since June), Leticia T. Moreno and Guillermo Pita.

## Highlights

The Unit has implemented a variety of high-throughput methods and covers an entire spectrum of projects offering:

- *Whole-genome genotyping* – microarrays of up to millions of markers for genome-wide association studies, copy number analysis, LOH analysis and whole genome methylation measurement. These arrays are used not only in normal tissue but also in tumour tissue
- *Medium-density genotyping* – targeted/custom assays for SNP genotyping as well as quantitative methylation measurements in specific genes, in human and other species
- *Low-density genotyping* – assays individual loci or small sets of genes by allelic discrimination

The Unit also advises researchers on study design and statistical analysis, offering support for marker selection in custom arrays and tools for SNP and CNV analysis.

Our research is focused on the identification of genetic factors influencing efficacy and toxicity of anticancer drugs. Recently we studied the association between the appearance of severe hand-foot syndrome (HFS) – one of the most relevant

dose-limiting adverse effects of capecitabine treatment – and polymorphisms in genes from drug metabolic pathways. We showed that increased allele-specific expression of a deletion in the cytidine deaminase promoter was significantly associated with an increased risk of capecitabine-induced HFS (OR= 0.51, 95%CI 0.27-0.95, p=0.028). We are currently validating this finding in an independent group of patients enrolled in a clinical trial of capecitabine (in collaboration with M. Martín, Head of Oncology Services, the *Hospital Gregorio Marañón*, Madrid, and Roche Company).

In addition, thanks to funding support from the *Asociación Española contra el Cáncer (AECC)*, we have developed the Spanish Pharmacogenetics Network for Paediatric Oncology. Ten major Spanish paediatric hospitals in the network are registering Adverse Drug Reaction (ADR) cases with highly relevant clinical data.

## Publications

Sherborne AL, et al. (2010). Variation in *CDKN2A* at 9p21.3 influences childhood acute lymphoblastic leukemia risk. *Nat Genet* 42, 492-494.

Castillo SD, et al. (2010). Gene amplification of the transcription factor DP1 and *CTNND1* in human lung cancer. *J Pathol* 222, 89-98.

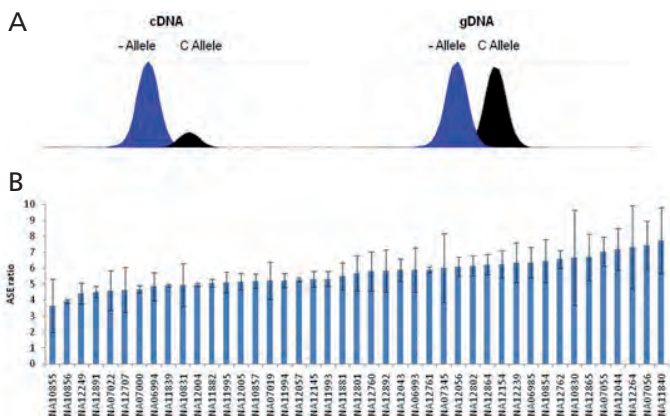
Galvan A, Falvella FS, Frullanti E, Spinola M, Incarbone M, Nosotti M, Santambrogio L, Conti B, Pastorino U, Gonzalez-Neira A, Dragani TA (2010). Genome-wide association study in discordant sibships identifies multiple inherited susceptibility alleles linked to lung cancer. *Carcinogenesis* 31, 462-465.

Rosa-Rosa JM, et al. (2010). Deep sequencing of target linkage assay-identified regions in familial breast cancer: methods, analysis pipeline and troubleshooting. *PLoS One* 5, e9976.

Fletcher O, et al. (2010). Missense variants in *ATM* in 26,101 breast cancer cases and 29,842 controls. *Cancer Epidemiol Biomarkers Prev* 19, 2143-2151.

Landa I, et al. (2010). Allelic variant at -79 (C>T) in *CDKN1B* (p27Kip1) confers an increased risk of thyroid cancer and alters mRNA levels. *Endocr-Relat Cancer* 17, 317-328.

Ibarrola-Villava M, et al. (2010). Genetic analysis of three important genes in pigmentation and melanoma susceptibility: *CDKN2A*, *MCT1R* and *HERC2/OCA2*. *Exp Dermatol* 19, 836-844.



**Figure:** Allele-specific expression (ASE) analysis in heterozygous samples for CDD polymorphism (C/-). (A) Example of peaks obtained for the deleted allele (blue) and the C allele (black), for cDNA (left) and for genomic DNA (gDNA; right). (B) The ASE ratio was calculated by normalising the ratio between the peak areas of the two alleles in cDNA for the same ratio in the genomic DNA. The average value of ASE ratio for the deleted allele versus the C allele was 5.7 (range of 3.9-7.7; standard deviation=0.83).