HUMAN GENOTYPING-*CEGEN* UNIT

Anna González-Neira
Unit Head

Graduate Students
Hugo Tejera, Alejandro Velasco

Technicians
Charo Alonso, Núria Álvarez,
Belén Herráez, Rocío Nuñez (TS)*,
Guillermo Pita (TS)*

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OVERVIEW

In the Unit we implement high-throughput methods for detection of genetic variation (single nucleotide variants, indels, structural variants) and methylation analysis using DNA microarray and next-generation DNA sequencing technologies. Complementarily, research focused on identifying predictive biomarkers for precision medicine is undertaken.

"Our aim is to identify predictive biomarkers in cancer patients in order to implement precision medicine in clinical practice."

RESEARCH HIGHLIGHTS

Novel predictive genetic markers for adverse drug reactions in breast cancer (BC) patients. Persistent chemotherapy-induced alopecia (pCIA) and capecitabine-induced hand-foot syndrome (CiHFS) are 2 common adverse drug reactions in cancer treatment. pCIA occurs in its most severe form in up to 10% of BC patients treated with docetaxel-based therapies, having a profound psychological impact on them. CiHFS is a dermatological toxicity affecting around 30% of patients, and the main cause of dose reductions and chemotherapy delays. By GWAS, we identified a regulatory variant associated with pCIA appearance in patients; this finding was validated in the replication cohort (ORcombined 4.05; 95% IQR, 2.46-6.67; P=3.946 x 10^{-8}). This variant affects ABCB1 mRNA expression, being the risk allele associated with decreased expression. The ABCB1 gene encodes P-glycoprotein, an efflux pump responsible for the elimination of docetaxel, and lower expression could cause decreased drug elimination and thus its intracellular accumulation. Carriers of the risk allele would experience high drug exposure in the hair follicle and alopecia may become permanent, owing to the destruction of hair follicle stem cells. In addition, we discovered and replicated a cluster of 4 variants associated with decreased levels of CDH4 mRNA and the protein it encodes, R-cadherin, which localises in the granular layer of the epidermis. This resulted in reduced expression of involucrin, a protein of the cornified envelope, an essential structure for skin barrier function.

Identifying variants of pharmacogenomic interest using CSVS, a crowdsourcing database of the Spanish population genetic variability. Genetic differences between human populations are becoming increasingly recognised as important factors accounting for interindividual variations in drug responsiveness. Using data from the CSVS repository, we addressed how population-specific differences in genes involved in drug absorption, distribution, metabolism, excretion and toxicity (ADMET) could affect the rates and risks of drug inefficacy and/or adverse drug reactions in the Spanish population. We studied the Spanish genetic variability in a total of 421 pharmacogenes and, interestingly, a non-negligible percentage of private variation was observed in genes encoding proteins involved in drug metabolism, transport, and response.

Detection of mutations in liquid biopsies from paediatric CNS tumours. Paediatric CNS tumours are the most fatal cancer diseases in childhood. Due to their localisation and infiltrative nature, some tumour resections or biopsies are not feasible. We conducted the first study to compare different sources of liquid biopsies in paediatric cancers, an unmet need for clinical practice. We found serum to be more promising than plasma for BRAF V600E by dPCR detection in liquid biopsy of CNS paediatric cancers. ■

PUBLICATIONS

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