HUMAN GENOTYPING-*CEGEN* UNIT

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OVERVIEW

The most abundant types of genetic variation are single nucleotide variants (SNVs) and copy number variants (CNVs). Association studies involving the large-scale analysis of both SNVs and CNVs in thousands of patients can help to identify genes underlying complex diseases such as cancer, and drug responses. In this Unit we implement different high-throughput and cost-effective methods to measure from one to millions of SNVs and CNVs. In addition, epigenetic studies using whole-genome methylation arrays are performed in the Unit. Complementarily, research focused on the identification of biomarkers for precision medicine is also undertaken.

"Advances in understanding patients' responses to therapy will help to individualise cancer patient care."

RESEARCH HIGHLIGHTS

Identification of genetic variants associated with docetaxel and anthracycline efficacy

Taxanes and anthracyclines are widely used in the treatment of breast cancer, despite the benefit being limited to a small proportion of patients and that preoperative biomarkers, which are predictive of clinical outcome, still remain lacking. We carried out a pharmacogenetic study in 181 patients with locally advanced breast cancer, previously enrolled in a phase 2 randomised clinical trial (NCT00123929), in which patients were randomly assigned to receive doxorubicin (anthracycline) or docetaxel (taxane) neoadjuvant chemotherapy. We assessed whether genetic variants in 15 key transport or metabolism genes relevant to doxorubicin and docetaxel drugs could play a role as predictive biomarkers. We identified a genetic variant located in the promoter of ABCC2 as the strongest association with tumour response in patients treated with doxorubicin (P=0.009). We also identified a significant association for an intronic variant located in CYP1B1 associated with docetaxel tumour response ($P=2.15x10^{-4}$). Our integrated pathway-based approach enables the revealing of promising genetic biomarkers of treatment outcome in breast cancer patients.

New low-frequency variant loci associated with anthracycline-induced cardiotoxicity (AIC) in cancer patients by Illumina HumanExome Beadchip

Anthracycline chemotherapeutic agents are widely used in the treatment of cancer; however, chronic anthracycline-induced cardiotoxicity (AIC) is a serious long-term complication leading to substantial morbidity. Our aim was to identify new genes and low-frequency variants influencing the susceptibility to AIC. We studied the association of variants on the Illumina HumanExome BeadChip array in a discovery cohort of breast cancer anthracycline-treated patients. Using gene-based tests (SKAT-O) that have greater statistical power to detect rare variant associations and that can evaluate the cumulative effect of multiple genetic variants, we identified novel significant associations in a gene with a major role in mitochondrial fatty acid β-oxidation and the respiratory chain, involved in anthracycline-related toxicity via an oxidative stress mechanism. We replicated our association results in another cohort of anthracycline treated paediatric cancer patients from Spain.

Functional characterisation at the 20q13.33 risk locus for capecitabine-induced hand-foot syndrome (CiHFS)

Capecitabine is a chemotherapy drug widely used in breast and colorectal cancer; the most frequent adverse drug reaction to this treatment (in 30% of the patients) is CiHFS, a cause of dose reductions and dose delays. By genome-wide association studies (GWAS), we identified four linked *CDH4* regulatory variants (h2=risk haplotype) associated with the risk of CiHFS appearance ($HR=2.48\ p=1.43x10^{-8}$). The *CDH4* gene encodes R-Cadherin, which is localised in the granular layer of the epidermis and is involved in the cohesiveness of epithelial layers. We demonstrated that these regulatory variants are able to mediate chromatin structural changes in chromatin organisation, which results in the presence of the risk alleles and in decreased expression levels of CDH4 mRNA and R-Cadherin protein. Additional functional experiments are being performed. The study has been carried out in collaboration with CNIO's Chromosome Dynamics Group and the Epithelial Cell Biology Group. ■

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