

Pharmacogenetics of toxicity to fluoropyrimidines

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Adverse reactions (ADRs) to chemotherapy agents, which can lead to treatment discontinuations and to the loss of treatment lines, are one of the major issues in the treatment of colorectal cancer. Individual genetic variants affect susceptibility to these adverse reactions. Several polymorphisms have been identified although they still need validation due to controversial results. Furthermore, new genetic variants need to be identified to increase the prediction power of existing tests. The aim of our work is to validate previously identified polymorphisms and to identify new variants. Three different approaches were followed: an association study of previously identified SNPs with adverse reactions to capecitabine-based treatments in a cohort of colorectal cancer patients, an association study of tag-SNPs with adverse reactions to capecitabine-based treatments in the same cohort, and a whole exome study in eight colorectal cancer patients suffering from high toxicity to capecitabine-based treatments. Results validate several SNPs associated with ADR to capecitabine in CRC. A test can identify patients at high risk of severe overall toxicity more precisely than regular tests. Tag-SNPs allow identifying new SNPs related to ADR in fluoropyrimidine-treated patients. Finally, exome sequencing allows us to obtain a complete profile of genetic variants in exons, splice sites and 5' and 3' untranslated regions in all genes participating in fluoropyrimidine pathway. In summary, this global approach is an excellent way to increase the knowledge of fluoropyrimidine-related adverse reaction pharmacogenetics and to increase the predictive power of pharmacogenetic tests in this field.

Biography

Luis A Lopez-Fernandez is currently the Head of the Laboratory of Pharmacogenetics and Pharmacogenomics at Hospital General Universitario Gregorio Marañón in Madrid, Spain. He has completed his PhD from the University of Alcalá de Henares and Post-doctoral studies from Spanish Research Council and Centre de Biochimie (Nice, France). He is a Member of the Board of the Spanish Society of Pharmacogenetics and Pharmacogenomics. He was granted a Miguel Servet II position for young researchers. He has published more than 50 articles in international journals in the fields of Oncology, Genomics and Pharmacogenetics.

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