Description of mutations and functoin of a gene implicated in the development of Fanconi anemia and predisposition to ca

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An international research consortium, which included the participation of the Mutagènesi Group from the UAB, has made outstanding progress in the study of Fanconi anaemia. They have described the function and range of possible mutations of the gene implicated in this disease that affects functions like nerve and skeletal development, blood cell formation and predisposition to cancer.

This discovery will aid in detecting the defective gene that causes Fanconi anaemia, which is fundamental in prenatal diagnosis and even pre-implantation diagnosis where the objective is to select an embryo that is compatible with a transplant donor. Furthermore, identification of the responsible gene is indispensable for the future application of gene therapy.

The researchers have studied the function and mutational spectrum of the FANCD2 gene, one of thirteen genes implicated in Fanconi anaemia. The result is a step forward in the knowledge of the genetics and molecular biology of this disease which, although rare, is of important biomedical interest because the proteins that are implicated with it are also associated with different vital functions and cancer suppression. The work covers the molecular studies of all the D2 Fanconi patients (those affected by the Fanconi anaemia that present alternations of this gene) known around the world.

A more severe and rapid variant

This work also compared FANCD2 patients with 754 patients with FANCA, FANCC and FANCG, which are the more prevalent variants worldwide. The results indicate that the Fanconi D2 patients' symptoms (clinical phenotype) are more severe than the others.

This is due to the vital function of the FANCD2 gene in the maintenance of the stability of the genome and in the development and function of the multiple organs and tissues, such as the formation of white blood cells, platelets and other elements of the blood (Fanconi D2 patients have a dysfunction in the production of blood in the medulla starting at 2.4 years old on average), neuronal development (89% of the Fanconi D2 patients suffer from microcephalia) or the formation of skeletal tissue (72% of the Fanconi D2 patients present skeletal malformations). In addition, the progression of the disease is more rapid in Fanconi D2 patients resulting in the need for early transfusions for survival and transplants when there is a compatible donor.

Differences with animal models

On the other hand, the research shows that the mutations do not totally eliminate the FANCD2 gene function, but cause a low level of expression of the FANCD2 protein. These results indicate that in humans, as opposed to what was observed in mice, the total absence of the FANCD2 protein is impossible (without this protein the embryo will not develop), and underline the findings that animal models do not always reflect the clinical phenotype of the disease.

A consortium of 13 European and North American laboratories and hospitals performed the research, which included the group directed by Dr. Jordi Surrallés of the Departament de Genètica i de Microbiologia

(Department of Genetics and Microbiology) of the UAB and assigned to the Centro de Investigaciones Biomédicas en Red de Enfermedades Raras del Instituto de Salud Carlos III (CIBER-ER) (Biomedical Research Centre for Rare Diseases of the Carlos III Health Institute network). The American Journal of Human Genetics published the results in their May edition.

This study, together with others published by Dr. Surrallés' team complements a model study described in the May edition of the review Cell Cycle that relates the genetic base of the disease with its clinical heterogeneous progression. This model is based on the fact that the patients with a total absence of FANCA protein, whose main function is to activate FANCD2 protein, have a milder clinical phenotype than FANCD2 patients. In turn, these are milder than patients with FANCD1/BRCA2, a gene that acts directly on a DNA level and promotes repairs in cases of genetic mutations.

Source: Universitat Autònoma de Barcelona