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New study identifies 40 genes susceptible to migraine

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Migraine is one of the most common neurological disorders and it affects 1 out of 7 people in the world. Painful and incapacitating, it has multi-factor origins, with the participation of environmental triggering factors and several altered genes in each individual. Up to this date only 13 migraine-related genes were known and now a study of *Nature Genetics* proves the contribution of these 10 genes and adds 28 more to the candidate list.

In the international work, focused on the analysis of common genetic migraine variants on people, there is the participation of Professor Bru Cormand and the collaborator Cèlia Sintas, from the Department of Genetics, Microbiology and Statistics and the Institute of Biomedicine of the University of Barcelona (IBUB).

Migraine: a genetic risk factor on Chromosome X

Only a minority of migraine victims receive the proper diagnoses and treatment. According to the World Health Organization (WHO), this painful and incapacitating pathology has a big impact on public health and it is the 6th cause of incapacity in the world. In the phenotype expression, the pathology is described with the diagnostic criteria of the International de Cefalees society (IHS).

The new study broadens the range of the migraine genetic landscape with the finding of around 40 genes susceptible to the disease. Furthermore, the experts identified for the first time a genetic risk factor on the sexual chromosome X, a finding of biomedical interest since migraine is more common in women than men. This is the most ambitious multi-central study at a genome scale until the moment and it has been carried out with 59.674 patients of the pathology and 316.078 control individuals. The scale of this new international work has allowed detecting genetic variants which have an individual contribution to the phenotype but if combined, they can have a relevant role in the course of the pathology.

An unknown and underestimated pathology

According to Professor Bru Cormand, "The great news is the big size of demonstration: around 400.000 people, from whom 60.000 are migraine victims. This makes the results more reliable" said the expert, who is also member of the CIBER of Rare Diseases (CIBERER) and the Research Paediatrics Institute - Hospital Sant Joan de Déu (IRP-HSJD).

The new work contributes to a proper definition of the predisposing genetic factors on migraine through the case-control genome-wide association studies (GWAS). This methodology allows identifying genetic variants which are risk-common at a big scale (they show a higher frequency in the patient group than in controls).

This multi-central study has been carried out by the experts Ben Neale (Broad Institute, Boston), Jes Olesen (University of Copenhague), Daniel Chasman (Harvard Medical School, Boston), Dale Nyholt (Queensland University of Technology, Australia) and Aarno Palotie (Broad Institute, Boston), who coordinates the International Headache Genetics Consortium (IHGC). The Catalan node of the consortium is made up by experts of the Vall d'Hebron Hospital and the Faculty of Biology of the University of Barcelona, a team which collaborated with the Consortium in identifying other genes susceptible to migraine *(Nature Genetics,* 2012).

Vascular dysfunctions, the migraine's target

There is no scientific consensus on the origins of migraine as a vascular or neuronal dysfunction provoking vascular effects yet. According to the new study, the vascular hypotheses would stand out in the etiology of the disease. "Most of the found genetic risk factors are related to vascular functions or smooth muscle tissues -of non-voluntary contraction- like the one from peripheral venous blood. Therefore, although they do not rule out neuronal mechanisms on migraine -some of the identified genes are specifically active in the brain- it looks like the pathology would be caused by vascular reasons, mainly" said Professor Cormand.

Migraine with aura *versus* migraine without aura

The study focuses on the most prevalent forms of migraine: migraine without aura (the most common one, with cephalic episodes linked to nausea or hypersensitivity to light and sound) and migraine without aura, which goes

with visual alterations, weakness, etc. apart from other symptoms similar to non-aura episodes.

"Studying people with migraine with aura and people with non-aura migraine separately, we can only see genetic risk factors in the second type. In migraine without aura cases, there is no significant genetic risk factor, but that would be due a size problem or study design, since studies have only been carried out on common genetic alterations, and the rare ones could also play an important role" says Cormand.

"The new international work focuses on the definition of the genetic landscape of the common migraine, without focusing on the development of new therapies. However, the fact that lots of identified genes share the same role in the vascular function shows a clear path of clinic research" finished Cormand.

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