The first genetic factor for the 'common' migraine

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The analyse of the genome of 50,000 people has enabled an international team of researchers to discover a genetic particularity which is more common in migraine sufferers. It is the first categorical genetic link for migraines, with or without aura, the most common forms of this disease. The ULg has contributed to gathering 10% of the data required for this study.

Migraine is a widespread complaint which affects over 10% of the population, and three times as many women as men (read the article Migraine: its multiple facets). Despite its great prevalence and the numerous scientific studies which have been and continue to be carried out in order to better understand its origins and to treat it better, migraine is still keeping its mysteries to itself, notably in terms of the genetic mechanisms involved in its triggering.

Many types and sub-types of migraine exist, amongst which we find familial hemiplegic migraine, a rare sub-type of this affliction. If researchers have succeeded in placing their finger on several mutations of the genes responsible for familial hemiplegic migraine, their efforts have been in vain up until now as far as more common forms of migraine are concerned.

But recently, an international team of scientists have brought to light the first genetic particularity for migraine susceptibility, with or without aura, the most common forms of this disease. The results of this study were published at the end of August in the journal Nature Genetics (1). 'It is the first irrefutable genetic link concerning the most frequent forms of migraine,' explains Professor Jean Schoenen, Director of the ULg's Headache Research Unit (Department of Neurology and GIGA-Neurosciences), and one of the authors of this study, who participated in it in the framework of the European 'Eurohead' project. 'Links to at
least 18 chromosomal sites have been suspected for migraine sufferers, but these associations have never been replicated until now, and remain suspect,' continues Jean Schoenen.

**Bringing together the work effected beyond borders**

In order to be able to affirm the existence of a link between the presence of a genetic particularity in the human genome and a heightened susceptibility to migraine, an analysis of the DNA of a very large number of migraine patients is required. In addition it is necessary that the results obtained can be replicated. And it is precisely that that the researchers from 40 research centres in Europe have managed to do. In pooling their efforts they have in effect been able to study the genetic data of over 50,000 individuals and thus compare a very large number of the genomes of the people suffering from migraines and those of 'healthy' people.


'The ULg’s patient cohort represents 10% of the whole of the data and has served to confirm what has been brought to light amongst the patient cohorts in Finland and Germany,' specifies Jean Schoenen. 'We selected patients suffering exclusively from migraine with aura whose attacks began with visual disorders and which represent 20% of migraines. That represents a lot of work as it was at first necessary to ensure a precise diagnosis, identify the clinical characteristics of migraine patients, enter them into a database and obtain their informed consent. We then carried out, at our Citadelle CHR consultancy, blood sampling, whose DNA was extracted at the Liège CHU Molecular Genetics Laboratory and sent to the Netherlands for analysis,' points out the Professor.

In order to discover genes of other regions of the genome likely to be involved in migraines, the researchers examined with a fine toothcomb over 400,000 genetic markers - easily detectable DNA sequences - within the patients' DNA. 'Out of the hundreds of thousands of markers, only one was revealed to be found significantly more frequently in migraine patients, and particularly those with attacks of migraine with aura,' explains Jean Schoenen. If the scientists were also able to detect other interesting genetic markers, the statistical analyses did not reveal a convincing link between them and migraine.
When this study was published at the end of August the various media outlets spread the information widely, announcing the discovery of the 'first migraine gene.' In reality, the DNA sequence brought to light by the scientists is not a gene but a region called 'intergenic' situated on chromosome 8. 'This genetic footprint is situated between two genes whose function is known,' specifies the headache specialist.

What role is played by this region and why is its mutation susceptible to helping bring about migraines in people who carry it? 'Finnish researchers have shown that when they insert the polymorphism of this region, detected in migraine patients, into lymphoid cells, it interacts with the two genes around it and which are involved in glutamate regulation,' replies Jean Schoenen. Glutamate is the most widespread neurotransmitter exciter in the central nervous system. When glutamate is liberated in a neurone in the synaptic cleft, this neurotransmitter will link itself to the receptors situated on the following neurone and cause its excitation. Glutamate is thus an important actor in the transmission of nerve impulses between the neurones but if it accumulates in the synaptic cleft it could trigger pathological effects.

To avoid that, glial cells called 'astrocytes' are charged with recapturing glutamate within the synapses. 'These cells are provided with proteins which allows them to capture and recycle excess glutamate,' picks
up Professor Schoenen. 'And one of these proteins is coded by the intergenetic region which has a genetic anomaly in people suffering from migraines.'

**Poor glutamate control, a common point between epilepsy and migraine?**

There follows from these results the following hypothesis: the genetic anomaly identified in the present study is at the root of poor regulation of glutamate concentrations in the synaptic clefts by the astrocytes and thus be one of the reasons for the abnormal brain excitability in migraine sufferers. According to Jean Schoenen, this could moreover explain why epilepsy and migraine attacks can occur in tandem in the same patients more than chance would have it (read the article The origin of certain epilepsies is now better understood). 'The people affected by migraines with aura are two or three times more at risk of being subject to epileptic attacks. A flaw in glutamate control by the astrocytes could be one of the common links between the two diseases,' points out the Professor. 'We have known since work carried out in our Unit over fifteen years ago that the brains of people affected by migraines respond excessively to external stimuli, even between migraine attacks,' continues Jean Schoenen. 'We wondered if glutamate played a role in this affliction. There have in addition been tests on medicines against migraine which act on glutamate receptors but up until now no molecule has reached the marketing stage.'

If the hypothesis proposed is confirmed these new data will enable scientists and pharmaceutical firms to look into new anti-migraine medicines which act in a more targeted manner on the glutamate system. The study recently published in *Nature Genetics* certainly represents a major breakthrough in the understanding of the origins of 'common' migraines, but 'it does not resolve the complex genetic problem of these complaints,' stresses Jean Schoenen. In effect, the risk of being a migraine sufferer for a person who carries the chromosome 8 genetic anomaly is only multiplied by 1.36. Migraine being a polygenic disease - in other words one whose susceptibility of developing depends on a combination of several genetic particularities - the objective now is to discover other regions of the human genome involved it its manifestation.