

microRNA expression profile in migraine: the microMIG study

Summary

Migraine is a complex brain disorder and is the second most disabling neurologic condition overall. Multiple factors, including both genetic and environmental mechanisms seem to play a role in migraine. Migraine has a polygenic heritability pattern, in the latest GWAS meta-analysis 39 loci have been related to common migraine. However, the effect size of each individual reported gene is relatively modest and most of these genes have regulatory effects on gene expression rather than protein coding.

Environmental factors may modulate the expression of DNA. Therefore, the study of epigenetics which are the environmental influenced genetic regulatory mechanisms could provide further understanding of migraine pathophysiology; as well as, giving insight to the dynamic aspect of the disease specifically contributing to the migraine chronification.

Among the epigenetic regulatory mechanisms, microRNAs (miRNA) are a subtype of noncoding RNA of ~22 nucleotides long that act as key regulators of genetic expression by inhibiting transcription or promoting degradation of selected messenger RNAs (mRNAs). A single miRNA sequence could regulate multiple mRNA, exerting a pleiotropic modulation of cellular processes. Moreover, it has been stated that miRNA could help mediate the environmental induced changes in genetic expression. miRNA have been found intracellularly and in all body fluids, including plasma, saliva and urine.

Accessing the central nervous system is too invasive so, peripheral blood mononuclear cells (PBMC) are an indirect measure of changes that might be going on in the brain. Their gene expression can reflect brain changes, as multiple CNS processes, including neurotransmitters and hormones, interact with the cells of the immune system. For instance, differential miRNA expression profiles have been identified in chronic pain conditions, psychiatric conditions, and neurological disorders.

So, in migraine we have found after of having done all of this exploratory analysis, we have found that there is a characteristic miRNA profile after doing all of the initial exploratory and replication study. After this, the next steps will be to validate this is a larger, more heterogenous international cohort.

Hypothesis vs. Findings

Our hypothesis is that in changes in the miRNA expression profiles of PBMC may signal, and possibly mediate, the changes of the brain in migraine. Hence, the goal of the study is to find differentially expressed miRNAs in PBMC of episodic (EM) and chronic migraine (CM) patients compared to healthy controls.

With this hypothesis we designed and performed an epigenetic case control study to compare the expression of miRNA in PBMC among patients with CM, EM and healthy control using miRNA microarrays.

For this exploratory study, RNA was extracted from 150 patients (CM 52, EM 46, HC 52) that fulfilled the inclusion criteria. The mean RIN for the samples included in the analysis was: CM 7.4 ± 0.9 , EM 7.4 ± 0.9 , Healthy controls 7.3 ± 0.9 . In order to compare miRNA results clinical differences (in CM patients were significantly older than HC (HC: 33.7 ± 11.4 vs. CM: 40.0 ± 12.3) and scored higher in stress and depression we considered as covariates in the analysis.

We found a specific profile of miRNAs in migraine, specifically: 5 significant miRNA DE between healthy control and all migraineurs (CM+EM), 10 between control and CM, and 8 between controls and EM, which represented the basis for the classification analysis.

Unanswered Questions

In our study, we have arrived to the results that we expected. After this, we will continue to complete the findings by replicating our results first in a local cohort and then in a larger, more heterogenous international cohort. Our goal is to find a final microRNA signature for migraine. We will work with perseverance and interest to find this.

What this research means to you

The Migraine Research Foundation has allowed us to put the first steps in this migraine epigenetics project. For us this was very important, as it proofed that the idea was interesting enough to develop further.

We have achieved what we expected and will continue working in this line of research to be able to arrive to the point where these findings have an impact both on helping us better understand the pathophysiology of migraine and have a translational impact on our patients.