

[Financial stress is associated with migraine, if you have specific circadian gene variants](#)

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People with a specific variation in the CLOCK gene have more migraines under financial stress. This work, the first time that the genetics of circadian rhythms has been shown to have an effect on migraine, is presented at the ECNP conference in Paris.

Migraine is a serious and debilitating neurological disease affecting 1 billion people worldwide. Migraine has been estimated to cause a financial cost of around €27 billion every year in the European Union, and \$17 billion every year in the USA*. In the UK, 1 in 4 women and 1 in 12 men are migraine sufferers.

The background of migraine is highly complex involving a large number of genes and their interaction with environmental effects, and acting via multiple pathways in the central nervous system. Variations of circadian genes (which affect how the body controls and responds to environmental changes – such as changes in light) have previously been shown to affect mood disorders, so it was thought it would be interesting to see if they were associated with migraine.

The group of researchers from Hungary and the UK checked 999 patients from Budapest and 1350 from Manchester, for two variants (*single nucleotide polymorphisms, SNPs*) of the CLOCK gene, and how these are associated with migraine. The CLOCK gene has an important role in regulating many rhythmic patterns of the body, including body temperature or level of cortisol, the primary stress hormone. They found that there was no significant direct connection between the gene and migraine, but when they factored in stress (financial stress, measured by a financial questionnaire), they showed that the investigated gene variants increased the odds of having migraine type headaches in those subjects who suffered from financial hardship by around 20%. (odds ratio – see abstract for details).

The researchers looked at functional single nucleotide polymorphisms within the CLOCK gene that are able to influence how much protein is transcribed from the gene. Because this protein controls the body clock machinery these variants may impair processes that can prevent migraine in the face of stress.

Researcher Daniel Baksa (Semmelweis University, Budapest) said:

"This work does not show what causes migraine – there is no single cause – but it does show that both stress and genetics have an effect. In the work presented here, we were able to show that stress – represented by financial hardship – led to an increase in migraine in those who have a particular gene variant. What we need to do now is to see if other circadian gene variants in association with different stress factors cause the same effect.

The strength of our study is that we saw the same effect in two independent study groups, in Budapest and Manchester, so we think it is a real effect. The investigated gene variants are present

in around 1/3 of the population, so they are common variants with small effect size. Our results shed light on one specific mechanism that may contribute to migraine. What it does mean is that for many people, the stress caused by financial worries can physically affect you. Migraine involves a huge health and financial burden each year, so any steps we can take to help patients understand their condition will be really welcome.”

Commenting, Professor Andreas Reif (University Hospital, Frankfurt) said:

“This is a really interesting study on the interaction of genetics with stress in migraine. The studied gene is involved in the circadian system, which has previously been shown to be implicated in mental disorders such as bipolar disorder, which intriguingly is comorbid with migraine. Thus, this study might provide a clue how these diseases might be linked on the genetic level which is interesting as such. But even beyond this, the study demonstrates how an environmental risk factor exerts its effect only in the presence of a given genetic risk factor. This has not been done to a great extent in migraine, making this study an exciting new lead.”

*See <https://www.news-medical.net/health/Economic-Impact-of-Migraines.aspx>

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Notes for Editors

[Please mention the ECNP Conference in any story resulting from this press release](#)

The European College of Neuropsychopharmacology (ECNP)

The ECNP is an independent scientific association dedicated to the science and treatment of disorders of the brain. It is the largest non-institutional supporter of applied and translational neuroscience research and education in Europe. Website: www.ecnp.eu

The 30th annual ECNP Congress takes place from 2nd to 5th September in Paris. It is Europe’s premier scientific meeting for disease-oriented brain research, annually attracting between 4,000 and 6,000 neuroscientists, psychiatrists, neurologists and psychologists from around the world. Congress website: <http://2017.ecnp.eu/>

P.1.a.004 Financial hardship may trigger migraine through circadian dysregulation – a possible role for the CLOCK gene

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For full affiliations see ‘programme’ section of conference website:

Objectives Patients with mood disorder often show biological rhythm-related symptoms, and evidence suggest connection between mood disorders and different circadian genes [1]. There is a well-known comorbidity between migraine and mood disorders, with an overlap in their genetic factors [2], and migraine attacks are frequently triggered by different external and internal changes in rhythmicity – such as stress, hormonal fluctuations, weather changes, sleep deprivation and other alterations of daily routine [3]. Therefore, circadian genes could also play a role in migraine. The CLOCK gene is a central component of the circadian clock, a transcriptional activator effecting the transcription of downstream circadian genes; and it has been associated with mood disorders [1], thus it’s a good candidate gene for migraine, too. Our goal was to test two functional SNPs of the circadian CLOCK gene (rs10462028 and rs3749474) to identify their possible influence on migraine.

Methods 2349 subjects (720 males and 1629 females) were recruited through general practices and advertisements from Manchester (n=1350) and Budapest (n=999) (aged between 18 and 60). The probability of migraine status was measured by the ID-Migraine Questionnaire. Chronic stress was defined by financial status derived from the background

questionnaire of the study. Genomic DNA was extracted from buccal mucosa cells. The main effect of the CLOCK gene SNPs and the SNPs x chronic stress interaction effects were tested on migraine using logistic regression models with additive, dominant and recessive models in the total population and in both subpopulations. All statistical models were adjusted for population, gender and age. Statistical analyses were made using PLINK 1.9 and IBM SPSS Statistics 23.

Results None of the SNPs showed main genetic effects on possible migraine, but both of them showed significant interaction with financial status on possible migraine (for rs10462028: OR= 0.79, $p<0.001$; for rs3749474: OR=1.22, $p<0.05$). The significant effects of the SNPs (except one) were replicated in the subpopulations (in Manchester: for rs10462028: OR=0.52, $p<0.05$; for rs3749474: not significant; and in Budapest: for rs10462028: OR=0.6, $p<0.001$; for rs3749474: OR=1.6, $p<0.05$).

Conclusions Our results suggest that the CLOCK gene might have a role in migraine in the presence of chronic stress represented by financial hardship. Thus, financial difficulties may trigger migraine by influencing circadian rhythmicity. Dysregulation of the circadian clock has also been implicated in the pathogenesis of various diseases (such as seasonal affective disorder, hypertension, asthma and cancer) [4], therefore a stress-elicited circadian dysregulation in migraineurs could be a factor in the onset of other illnesses, too. The investigated SNPs in the CLOCK gene affect miRNA binding, and evidence suggest that miRNAs have a distinct role in clock physiology, therefore they present novel therapeutic targets for diseases related to the circadian rhythm [4]. Further investigation of the potential functions of circadian genes in the pathophysiology of migraine, especially in patients with serious life stressors, may provide new treatment strategies.

References – from press officer

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How this was reviewed?

After initial approval from the ECNP media group, the press release was developed by the press officer and the author, with the final version being approved by the ECNP media review group. We then sought an additional view and comment from someone with expertise in the field – this is the person who comments in the press release. None of the reviewers have been involved in the work.