First genetic link to common migraine exposed

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A world-wide collaboration of researchers has identified the first-ever genetic risk factor associated with common types of migraine. The researchers, who looked at the genetic data of more than 50,000 people, have produced new insights into the triggers for migraines attacks and they hope their research will open the door for novel therapeutics to prevent migraine attacks.

The team found that patients with a particular DNA variant on Chromosome 8 between two genes - PGCP and MTDH/AEG-1 - have a significantly greater risk for developing migraine. The team also discovered a potential explanation for this link. It appears that the associated DNA variant regulates levels of glutamate - a chemical, known as a neurotransmitter, which transports messages between nerve cells in the brain. The results suggest that an accumulation of glutamate in nerve cell junctions (synapses) in the brain may play a key role in the initiation of migraine attacks. Prevention of the build up of glutamate at the synapse may provide a promising target for novel therapeutics to ease the burden of the disease.

Migraine affects approximately one in six women and one in twelve men, and has been estimated to be the most expensive brain disorder to society in the EU and US. A US report measures its economic costs as similar to those of diabetes and WHO lists it as one of the top 20 diseases with years lived with disability (YLDs).

Although researchers have in the past described genetic mutations giving

rise to rare and extreme forms of migraine, this is the first time a team has identified a genetic variant giving rise to the common form of the condition.

"This is the first time we have been able to peer into the genomes of many thousands of people and find genetic clues to understand common migraine," said Dr Aarno Palotie, chair of the International Headache Genetics Consortium at the Wellcome Trust Sanger Institute, which spearheaded the study.

"Studies of this kind are possible only through large-scale international collaboration - bringing together the wealth of data with the right expertise and resources - so that we could pick out this genetic variant. This discovery opens new doors to understand common human diseases."

The researchers carried out what is known as a genome-wide association study (GWAS) to zoom in on genome variants that could increase susceptibility to migraine. The team compared the genomes of more than 3000 people from Finland, Germany and The Netherlands with migraine with the genomes of more than 10,000 non-migraineurs, recruited from pre-existing studies, to spot differences that might account for one group's increased susceptibility to migraine. To confirm their link, the team compared the genomes of a second group of more than 3000 patients with more than 40,000 apparently healthy people.

The statistical analysis revealed that a DNA variation found between the PGCP and MTDH/AEG-1 genes on chromosome 8 appears to be associated with increased susceptibility to common migraine. The variant appears to alter the activity of MTDH/AEG-1 in cells, which regulates the activity of the EAAT2 gene: the EAAT2 protein is responsible for clearing glutamate from brain synapses in the brain. EAAT2 has previously been linked with other neurological diseases, including epilepsy, schizophrenia and various mood and anxiety

disorders.

"Although we knew that the EAAT2 gene has a crucial role to play in neurological processes in human and potentially in the development of migraine, until now, no genetic link has been identified to suggest that glutamate accumulation in the brain could play a role in common migraine," says co-senior author of the study Professor Christian Kubisch of University of Ulm, Germany (previously at the University of Cologne where he conducted his research for this study.) "This research opens the door for new studies to look in depth at the biology of the disease and how this alteration in particular may exert its effect."

The authors caution that further study will be needed, both into the DNA variant and its regulatory effect on the genes flanking it, to shed light on the mechanism for the occurrence of migraine attacks, and further research to find additional contributing genetic factors. The authors also suggest that broader population samples should be interrogated.

"Although the patients in the study were all diagnosed with common migraine, they were largely recruited from specialist headache clinics," says and Dr Gisela Terwindt of Leiden University Medical Center, another senior author of the study. "Because they are attending headache clinics they are likely to represent only the more extreme end of those who suffer common migraine. In the future, we should look at associations across the general population, including also people who are less severely affected."

A collaboration between more than 40 centres from around the world, steered by the International Headache Genetics Consortium (www.headachegenetics.org/index.html), produced the findings.

More information: Anttila, V et al. (2010) Genome-wide association study of migraine implicates a common susceptibility variant on 8q22.1.

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