# migraine with aura and homocysteine derivatives



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(Updated 9/4/04)

Nouchine Hadjikhani, Margarita Sanchez del Rio, Ona Wu, Denis Schwartz, Dick Bakker, Bruce Fischl, Kenneth K. Kwong, F. Michael Cutrer, Bruce R. Rosen, Roger B. H. Tootell, A. Gregory Sorensen, and Michael A. Moskowitz

## Mechanisms of migraine aura revealed by functional MRI in human visual cortex

PNAS 98: 4687-4692; published online before print as 10.1073/pnas.071582498

"Cortical spreading depression (CSD) has been suggested to underlie migraine visual aura. However, it has been challenging to test this hypothesis in human cerebral cortex. Using high-field functional MRI with near-continuous recording during visual aura in three subjects, we observed blood oxygenation level-dependent (BOLD) signal changes that demonstrated at least eight characteristics of CSD, time-locked to percept/onset of the aura. Initially, a focal increase in BOLD signal (possibly reflecting vasodilation), developed within extrastriate cortex (area V3A). This BOLD change progressed contiguously and slowly (3.5 +/- 1.1 mm/min) over occipital cortex, congruent with the retinotopy of the visual percept. Following the same retinotopic progression, the BOLD signal then diminished (possibly reflecting vasoconstriction after the initial vasodilation), as did the BOLD response to visual activation. During periods with no visual stimulation, but while the subject was experiencing scintillations, BOLD signal followed the retinotopic progression of the visual percept. These data strongly suggest that an electrophysiological event such as CSD generates the aura in human visual cortex." [Full Text]

Lauritzen M.

## Pathophysiology of the migraine aura. The spreading depression theory.

Brain. 1994 Feb;117 ( Pt 1):199-210.

"The characteristic form and development of sensory disturbances during migraine auras suggests that the underlying mechanism is a disturbance of the cerebral cortex, probably the cortical spreading depression (CSD) of Leao. The demonstration of unique changes of brain blood flow during attacks of migraine with aura, which have been replicated in animal experiments during CSD, constitutes another important line of support for the 'spreading depression' theory, which may be a key to an understanding of the migraine attack. Cortical spreading depression is a short-lasting depolarization wave that moves across the cortex at a rate of 3-5 mm/min. A brief phase of excitation heralds the reaction which is immediately followed

Görtz P, Hoinkes A, Fleischer W, Otto F, Schwahn B, Wendel U, Siebler M

## Implications for hyperhomocysteinemia: not homocysteine but its oxidized forms strongly inhibit neuronal network activity.

J Neurol Sci. 2004 Mar 15;218(1-2):109-14.

Severe hyperhomocysteinemia (50-200 microM) often presents itself with acute neuronal dysfunction including seizures and psychosis. Its moderate form (15-50 microM) is associated with cognitive impairment and dementia. We investigated the neuropharmacological effects of homocysteine and its oxidized forms, homocysteinesulfinic acid (HCSA) and homocysteic acid (HCA), on neuronal network function utilizing dissociated cortical neurons from embryonic Wistar rats on microelectrode arrays. All substances inhibited dose-dependently and reversibly spontaneous neuronal network activity within seconds: L-HCSA and L-HCA blocked spontaneous spike rate (SSR) significantly at very low concentrations, with an IC50 of 1.9 and 1.3 microM, respectively; whereas the dose-response curve of D,L-homocysteine revealed an IC50 of 401 microM. These effects were antagonized by 2-amino-5-phosphonovaleric acid (APV) pointing to the NMDA receptor as mediator of this fast and reversible inhibition of network activity. We conclude that a neuronal dysfunction observed in hyperhomocysteinemia is likely due to HCSA and HCA since effective concentrations of homocysteine are not reached in patients. [Abstract]

Lea RA, Ovcaric M, Sundholm J, MacMillan J, Griffiths LR

## The methylenetetrahydrofolate reductase gene variant C677T influences susceptibility to migraine with aura.

BMC Med. 2004 Feb 12;2(1):3.

BACKGROUND: The C677T variant in the methylenetetrahydrofolate reductase (MTHFR) gene is associated with increased levels of circulating homocysteine and is a mild risk factor for vascular disease. Migraine, with and without aura (MA and MO), is a prevalent and complex neurovascular disorder that may also be affected by genetically influenced hyperhomocysteinaemia. To determine whether the C677T variant in the MTHFR gene is associated with migraine susceptibility we utilised unrelated and family-based case-control study designs. METHODS: A total of 652 Caucasian migraine cases were investigated in this study. The MTHFR C677T variant was genotyped in 270 unrelated migraine cases and 270 controls as well as 382 affected subjects from 92 multiplex pedigrees. RESULTS: In the unrelated case-control sample we observed an over-representation of the 677T allele in migraine patients compared to controls, specifically for the MA subtype (40% vs. 33%) (chi2 = 5.70, P = 0.017). The Armitage test for trend indicated a significant dosage effect of the risk allele (T) for MA (chi2 = 5.72, P = 0.017). This linear trend was also present in the independent family-based sample (chi2 = 4.25, Padjusted = 0.039). Overall, our results indicate that the T/T genotype confers a modest, yet significant, increase in risk

by prolonged nerve cell depression synchronously with a dramatic failure of brain ion homeostasis, efflux of excitatory amino acids from nerve cells and enhanced energy metabolism. Recent experimental work has shown that CSD in the neocortex of a variety of species including man is dependent on activation of a single receptor, the N-methyl-D-aspartate receptor, one of the three subtypes of glutamate receptors. The combined experimental and clinical studies point to fruitful areas in which to look for migraine treatments of the future and provide a framework within which important aspects of the migraine attack can be modelled." [Abstract]

Gorji A, Scheller D, Straub H, Tegtmeier F, Kohling R, Hohling JM, Tuxhorn I, Ebner A, Wolf P, Werner Panneck H, Oppel F, Speckmann EJ.

## Spreading depression in human neocortical slices.

Brain Res. 2001 Jul 6;906(1-2):74-83.

"Cortical spreading depression (CSD) occurrence has been suggested to be associated with seizures, migraine aura, head injury and brain ischemia-infarction. Only few studies identified CSD in human neocortical slices and no comprehensive study so far evaluated this phenomenon in human. Using the neocortical tissue excised for treatment of intractable epilepsy, we aimed to investigate CSD in human. CSD was induced by KCl injection and by modulating T-type Ca(2+) currents in incubated human neocortical tissues in an interphase mode. The DC-fluctuations were recorded by inserting microelectrodes into different cortical layers. Local injection of KCl triggered single CSD that propagated at 3.1+/-0.1 mm/min. Repetitive CSD also occurred spontaneously during long lasting application (5 h) of the T-type Ca(2+) channel blockers amiloride (50 microM) or NiCl(2) (10 microM) which was concomitant with a reversible extracellular potassium increase up to 50 mM. CSD could be blocked by the N-methyl-D-aspartate receptor antagonist 2-amino-5-phosphonovaleric acid in all cases. The results demonstrate that modulation of the Ca(2+) dynamics conditioned human neocortical slices and increased their susceptibility to generate CSD. Furthermore, these data indicate that glutamatergic pathway plays a role in CSD phenomenon in human." [Abstract]

Faria LC, Mody I

**Protective Effect of Ifenprodil against Spreading Depression in the Mouse Entorhinal Cortex.**

J Neurophysiol. 2004 Jun 16;

In the brain, spreading depression (SD) is

for the MA subtype (odds ratio: 2.0 - 2.5). No increased risk for the MO subtype was observed (P > 0.05). CONCLUSIONS: In Caucasians, the C677T variant in the MTHFR gene influences susceptibility to MA, but not MO. Investigation into the enzyme activity of MTHFR and the role of homocysteine in the pathophysiology of migraine is warranted. [Abstract]

Oterino A, Valle N, Bravo Y, Muñoz P, Sánchez-Velasco P, Ruiz-Alegría C, Castillo J, Leyva-Cobián F, Vadillo A, Pascual J

## MTHFR T677 homozygosis influences the presence of aura in migraineurs.

Cephalalgia. 2004 Jun;24(6):491-4.

It has been suggested that folate metabolism could be involved in migraine pathogenesis. We analysed the 5',10'-methylenetetrahydrofolate reductase (MTHFR) genotypic distribution in a large migraine sample. We genotyped 230 migraine patients (152 migraine without aura (MO) and 78 migraine with aura (MA)) and 204 nonheadache controls. The incidence of TT homozygosis for migraine in general (12%), MO (9%) and MA (18%) did not significantly differ from that found in healthy controls (13%). Differences were significant when the frequency of TT homozygosis between MA and MO (P = 0.03, OR = 2.34, 95% CI = 1.04-5.26) was compared. There was a tendency for a higher frequency of the MTHFR T allele in the MA group (42%) as compared to MO (29%) and controls (36%). These differences were significant only in the case of MA vs. MO (P = 0.006, OR = 1.75, 95% CI = 1.15-2.65). These results could indicate that the MTHFR C677T polymorphism, causing mild hyperhomocystinaemia, might be a genetic risk factor for experiencing aura among migraineurs. Overall, however, there was no association between migraine and the C677T MTHFR polymorphism. [Abstract]

Kara I, Sazci A, Ergul E, Kaya G, Kilic G

## Association of the C677T and A1298C polymorphisms in the 5,10 methylenetetrahydrofolate reductase gene in patients with migraine risk.

Brain Res Mol Brain Res. 2003 Mar 17;111(1-2):84-90.

Although controversial, diminished activity of 5,10 methylenetetrahydrofolate reductase (MTHFR), a regulatory enzyme of homocysteine metabolism, may predispose to migraine in Turkish people. In a case-control study, we determined the prevalence of two common MTHFR polymorphisms,C677T and A1298C, in 102 migraine patients (23 migraine with aura, 70 migraine without aura and nine with tension-type headache) and compared it to that of 136 healthy controls. The frequencies of the T allele of MTHFR677 and the C allele of MTHFR1298 were significantly higher in the total migraine population (33.82%, 33.82%) than in controls (25.38% and 24.26%), respectively.The genotypes T677T and C1298C were the only genotypes significantly associated with migraine (OR=5.702; 95% CI=1.184-27.457; P=0.015) and (OR=8.933;

characterized by a large extracellular DC shift, a massive failure of ion homeostasis and a transient cessation of neuronal function. Clinically, SD is believed to be involved in various neurological disorders including migraine and cerebrovascular diseases. The propagation of cortical SD requires the release of glutamate, and NMDA receptors play a crucial role in this process. Here, we have isolated the NMDA-receptor-mediated component of extracellularly recorded field EPSPs (fEPSPs) in layers 2-3 of the entorhinal cortex of murine brain slices. In the absence of GABAA and AMPA receptor mediated synaptic transmission, stimulation of layer 6 afferents every 15 - 90 s elicited spontaneous SD on average within 18.5 min after the start of the stimulation. In the presence of ifenprodil, an NR2B receptor subunit-selective NMDA receptor antagonist, the occurrence of SD was nearly abolished. Our results are consistent with an important role of NR2B subunits in triggering SD in the entorhinal cortex. [Abstract]

Benz B, Grima G, Do KQ

## Glutamate-induced homocysteic acid release from astrocytes: possible implication in glia-neuron signaling.

Neuroscience. 2004;124(2):377-86.
Glial cells synthesise neuroactive substances and release them upon neurotransmitter receptor activation. Homocysteic acid (HCA), an endogenous agonist for glutamatergic N-methyl-D-aspartate (NMDA) receptors, is predominantly localised in glial cells. We have previously demonstrated the release of HCA from mouse astrocytes in culture following activation of beta-adrenergic receptors. Moreover, a release of HCA has also been observed in vivo upon physiological stimulation of sensory afferents in the thalamus. Here we report the glutamate-induced release of HCA from astrocytes. The effect of glutamate was mediated by the activation of ionotropic (NMDA and non-NMDA) as well as by metabotropic receptors. In addition, the release of HCA was Ca(2+)- and Na(+)-dependent, and its mechanism involved the activation of the Na+/Ca(2+)-exchanger. Furthermore, we provide evidence for the presence of functional NMDA receptors on astrocytes, which are coupled to an intracellular Ca2+ increase via stimulation of the Na+/Ca(2+)-exchanger. Our data thus favour a participation of glial cells in excitatory neurotransmission and corroborate the role of HCA as a "gliotransmitter." [Abstract]

Shi, Qi, Savage, Jason E., Hufeisen, Sandra J.,

95% CI=1.953-40.869; P=0.001), respectively). Individuals with migraine with aura with C1298C and C677C/C1298C genotypes were even more profoundly associated with migraine risk than others (OR=14.105; 95% CI=2.417-82.320; P=0.0001) and (OR=10.050; 95% CI=1.580-63.907; P=0.003), respectively. However individuals with migraine without aura with T677T and C1298C genotypes showed the same susceptibility (OR=7.444; 95% CI=1.503-36.863); P=0.005). Patients with C1298C and C677C/C1298C genotypes may also predispose to tension-type headache (OR=8.375; 95% CI=0.685-102.458); P=0.049).[Abstract]

Kowa H, Yasui K, Takeshima T, Urakami K, Sakai F, Nakashima K

## The homozygous C677T mutation in the methylenetetrahydrofolate reductase gene is a genetic risk factor for migraine.

Am J Med Genet. 2000 Dec 4;96(6):762-4.
Increased homocysteine levels are associated with various pathological conditions in humans, including stroke and cardiovascular disorders. Homocysteine acts as an excitatory amino acid in vivo and may influence the threshold of migraine headache. Frosst et al. [1995] reported an association between the homozygous C677T mutation in the 5,10-methylenetetrahydrofolate reductase (MTHFR) gene and serum homocysteine levels. This study was designed to determine the prevalence of the MTHFR mutation in Japanese patients with migraine and tension-type headache (TH). Seventy-four patients with migraine headaches (22 with aura and 52 without aura), 47 with THs, and 261 normal controls were recruited. Genotyping of MTHFR C677T polymorphism was performed by polymerase chain reaction-restriction fragment length polymorphism. We detected that the incidence of the homozygous transition (T/T) in migraine sufferers (20.3%) was significantly higher than that in controls (9.6%). Moreover, the frequency of the T/T genotype in individuals with migraine headaches with aura was remarkably high (40.9%). The MTHFR T allele was more frequent in the migraine group than in the control group. Our results support the conclusion that the MTHFR gene, causing mild hyperhomocysteinemia may be a genetic risk factor for migraine. [Abstract]

Santhosh-Kumar CR, Hassell KL, Deutsch JC, Kolhouse JF.

## Are neuropsychiatric manifestations of folate, cobalamin and pyridoxine deficiency mediated through imbalances in excitatory sulfur amino acids?

Med Hypotheses. 1994 Oct;43(4):239-44.
Folate, cobalamin and pyridoxine deficiency are associated with psychiatric or neurological symptomatology. Disturbances in sulfur amino acid metabolism leading to accumulation of homocysteine occurs in all three conditions as the metabolism of homocysteine depends on enzymes requiring these vitamins as cofactors. Oxidation products of homocysteine

Rauser, Laura, Grajkowska, Ewa, Ernsberger, Paul, Wroblewski, Jarda T., Nadeau, Joseph H., Roth, Bryan L.

**L-Homocysteine Sulfinic Acid and Other Acidic Homocysteine Derivatives Are Potent and Selective Metabotropic Glutamate Receptor Agonists**

J Pharmacol Exp Ther 2003 305: 131-142

"... because homocysteine is also involved in normal metabolic pathways of many biologically functional molecules, abnormalities in homocysteine metabolism may adversely affect many related and unrelated pathways which, in turn, cause diseases and disorders." [Full Text]

(homocysteine sulfinic acid and homocysteic acid) and cysteine (cysteine sulfinic acid and cysteic acid) are excitatory sulfur amino acids and may act as excitatory neurotransmitters, whereas taurine and hypotaurine (decarboxylation products of cysteic acid and cysteine sulfinic acid) may act as inhibitory transmitters. Homocysteic acid and cysteine sulfinic acid have been considered as endogenous ligands for the N-methyl-D-aspartate (NMDA) type of glutamate receptors. The profile of these sulfur amino acid neurotransmitters could be altered in a similar fashion in states of decreased availability of folate, cobalamin or pyridoxine. It is proposed that the mechanism of neuropsychiatric manifestations in all three conditions result from a combination of two insults to homocysteine catabolism in the brain. [Abstract]

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## Recent Migraine with Aura and Homocysteine Derivatives Research

1) Scher AI, Wu H, Tsao JW, Blom HJ, Feit P, Nevin RL, Schwab K

**MTHFR C677T Genotype as a Risk factor for Epilepsy Including Post-Traumatic Epilepsy in a Representative Military Cohort.**

J Neurotrauma. 2011 Jul 25;

The well-studied C677T variant in the methylenetetrahydrofolate reductase (MTHFR) enzyme is a biologically plausible genetic risk factor for epilepsy. First, plasma / serum levels of homocysteine, a pro-convulsant, are moderately elevated in individuals with the homozygote TT genotype. Further, the TT genotype has been previously linked with risk of migraine with aura - a comorbid condition - and with alcohol withdrawal seizures. Finally, several small studies have suggested that the TT genotype may be over-represented in epilepsy patients. In this study, we consider whether the MTHFR C677T or A1298C variants are associated with risk of epilepsy including post-traumatic epilepsy (PTE) in a representative military cohort. Study subjects were selected from the cohort of military personnel on active duty during the years 2003 through 2007 who had archived serum samples at the DoD Serum Repository - essentially all active duty personnel during this time frame. We randomly selected 800 epilepsy patients and 800 matched controls based on ICD-9-CM diagnostic codes. We were able to isolate sufficient genetic material from the archived sera to genotype approximately 85% of our study subjects. Odds of epilepsy were moderately increased in subjects with the TT vs. CC genotype (crude OR=1.52 [1.04-2.22], p=0.031; adjusted OR=1.57 [1.07-2.32], p=0.023). In our sensitivity analysis, risk was most evident for patients with repeated rather than single medical encounters for epilepsy (crude OR=1.85 [1.14-2.97], p=0.011, adjusted OR=1.95 [1.19-3.19], p=0.008) and particularly for PTE (crude OR=3.14 [1.41-6.99], p=0.005; adjusted OR=2.55 [1.12-5.80], p=0.026).

Our and earlier results suggest that the common MTHFR C677T variant may be a predisposing factor for epilepsy including PTE. Further exploration of baseline homocysteine and folate levels as predictors of seizure risk following traumatic brain injury is warranted. [PubMed Citation] [Order full text from Infotrieve]

2) Vázquez do Campo R, Morales-Vidal S, Randolph C, Chadwick L, Biller J
**[CADASIL: a case series of 11 patients].**
Rev Neurol. 2011 Feb 16;52(4):202-10.
[PubMed Citation] [Order full text from Infotrieve]

3) Isobe C, Terayama Y
**A remarkable increase in total homocysteine concentrations in the CSF of migraine patients with aura.**
Headache. 2010 Nov;50(10):1561-9.
[PubMed Citation] [Order full text from Infotrieve]

4) Nelson KB, Richardson AK, He J, Lateef TM, Khoromi S, Merikangas KR
**Headache and biomarkers predictive of vascular disease in a representative sample of US children.**
Arch Pediatr Adolesc Med. 2010 Apr;164(4):358-62.
[PubMed Citation] [Order full text from Infotrieve]

5) Bokhari FA, Shakoori TA, Hassan SA, Qureshi HJ, Qureshi GA
**Plasma homocysteine in patients of migraine without aura.**
J Ayub Med Coll Abbottabad. 2010 Apr-Jun;22(2):52-5.
[PubMed Citation] [Order full text from Infotrieve]

6) Michalak S, Rybacka J, Wysocka E, Kozubski W
**[The effect of tobacco smoking on the levels of circulating E-selectin in migraineurs].**
Przegl Lek. 2010;67(10):897-900.
[PubMed Citation] [Order full text from Infotrieve]

7) Termine C, Trotti R, Ondei P, Gamba G, Montani N, Gamba A, De Simone M, Marni E, Balottin U
**Mitral valve prolapse and abnormalities of haemostasis in children and adolescents with migraine with aura and other idiopathic headaches: a pilot study.**
Acta Neurol Scand. 2010 Aug;122(2):91-6.
[PubMed Citation] [Order full text from Infotrieve]

8) Gruber HJ, Bernecker C, Pailer S, Lechner A, Horejsi R, Möller R, Fazekas F, Truschnig-Wilders M
**Increased dopamine is associated with the cGMP and homocysteine pathway in female migraineurs.**

Headache. 2010 Jan;50(1):109-16.
[PubMed Citation] [Order full text from Infotrieve]

9) Oterino A, Toriello M, Valle N, Castillo J, Alonso-Arranz A, Bravo Y, Ruiz-Alegria C, Quintela E, Pascual J

**The relationship between homocysteine and genes of folate-related enzymes in migraine patients.**

Headache. 2010 Jan;50(1):99-168.
[PubMed Citation] [Order full text from Infotrieve]

10) Tietjen GE, Herial NA, White L, Utley C, Kosmyna JM, Khuder SA

**Migraine and biomarkers of endothelial activation in young women.**

Stroke. 2009 Sep;40(9):2977-82.
[PubMed Citation] [Order full text from Infotrieve]

11) Lea R, Colson N, Quinlan S, Macmillan J, Griffiths L

**The effects of vitamin supplementation and MTHFR (C677T) genotype on homocysteine-lowering and migraine disability.**

Pharmacogenet Genomics. 2009 Jun;19(6):422-8.
[PubMed Citation] [Order full text from Infotrieve]

12) Hamed SA

**The vascular risk associations with migraine: relation to migraine susceptibility and progression.**

Atherosclerosis. 2009 Jul;205(1):15-22.
Migraine is a common disorder in which changes in cortical excitability, neuroinflammation and dysfunction of the vascular wall contribute to its pathophysiology. Repeated attacks of migraine over prolonged periods result in inflammatory arteriopathy of the cranial vessels. Several studies indicate that migraine is associated with special pattern of inflammatory markers and some adverse vascular risk factors including: increased levels of CRP, ILs, TNF-alpha and adhesion molecules which are markers of systemic inflammation, oxidative stress and thrombosis, increased body weight, high blood pressure, hypercholesterolemia, impaired insulin sensitivity, high homocysteine levels, stroke and coronary heart disease. Such comorbidities are not explained by bias but indicate possible shared underlying pathogenic mechanisms. Recent studies have shown involvement of cranial as well as peripheral vascular dysfunction with migraine indicating that migraine may be a local manifestation of a systemic disease rather than a primary brain phenomenon. The associated inflammatory process of migraine together with the associated adverse medical comorbidities exposes patients to endothelial vascular wall injury which further increases migraine susceptibility and progression as well as increases the risk for atherogenesis. The knowledge that migraine is a risk for vascular diseases raises important clinical implications, recommendations and future perspectives in migraine treatment and prevention. [PubMed Citation] [Order full text from Infotrieve]

13) Ozdemir AO, Tamayo A, Munoz C, Dias B, Spence JD

**Cryptogenic stroke and patent foramen ovale: clinical clues to paradoxical embolism.**

J Neurol Sci. 2008 Dec 15;275(1-2):121-7.
[PubMed Citation] [Order full text from Infotrieve]

14) Moschiano F, D'Amico D, Usai S, Grazzi L, Di Stefano M, Ciusani E, Erba N, Bussone G

## Homocysteine plasma levels in patients with migraine with aura.

Neurol Sci. 2008 May;29 Suppl 1:S173-5.

We investigated homocysteine plasma levels in 136 MA sufferers and in 117 sex-and age-matched controls. Mean homocysteine plasma levels - as well as the proportion of subjects with hyperhomocysteinaemia - were significantly higher in patients with MA than in healthy controls. Hyperhomocysteinaemia may be a link between MA and ischaemic stroke. [PubMed Citation] [Order full text from Infotrieve]

15) Kurth T, Ridker PM, Buring JE

## Migraine and biomarkers of cardiovascular disease in women.

Cephalalgia. 2008 Jan;28(1):49-56.

Migraine has been associated with an unfavourable cardiovascular risk profile and with increased risk of cardiovascular disease. In a cross-sectional analysis of 27,626 women aged >or=45 years, we evaluated the association of migraine and migraine aura status with elevated levels of total cholesterol, low- and high-density lipoprotein cholesterol (HDL-C), non-HDL-C, apolipoprotein (Apo) A-1 and B(100), lipoprotein (a), C-reactive protein (CRP), fibrinogen, intercellular adhesion molecule-1, homocysteine and creatinine. A total of 5087 (18.4%) women reported any history of migraine. Compared with women with no migraine history, women who reported any history of migraine had modestly increased adjusted odds ratios (95% confidence interval) of 1.09 (1.01, 1.18) for elevated total cholesterol, 1.14 (1.05, 1.23) for non-HDL-C, 1.09 (1.01, 1.18) for Apo B(100) and 1.13 (1.05, 1.22) for CRP. The increase did not meaningfully differ according to migraine aura status and migraine frequency. In this large cohort of women, only a modest association was found between migraine and adverse levels of certain cardiovascular biomarkers. [PubMed Citation] [Order full text from Infotrieve]

16) Magis D, Allena M, Coppola G, Di Clemente L, Gérard P, Schoenen J

## Search for correlations between genotypes and electrophysiological patterns in migraine: the MTHFR C677T polymorphism and visual evoked potentials.

Cephalalgia. 2007 Oct;27(10):1142-9.

Interictally, migraineurs have on average a reduction in habituation of pattern-reversal visual evoked potentials (PR-VEP) and in mitochondrial energy reserve. 5,10-Methylenetetrahydrofolate reductase (MTHFR) is involved in folate metabolism and its C677T polymorphism may be more prevalent in migraine. The aim of this study was to search in migraineurs for a correlation between the MTHFR C677T polymorphism and the PR-VEP profile. PR-VEP were recorded in 52 genotyped migraine patients: 40 female, 24 without (MoA), 28 with aura (MA). Among them 21 had a normal genotype (CC), 18 were heterozygous (CT) and 13 homozygous (TT) for the MTHFR C677T polymorphism. Mean PR-VEP N1-P1 amplitude was significantly lower in CT compared with CC, and tended to be lower in TT with increasing age. The habituation deficit was significantly greater in CC compared with TT subjects. The correlation between the cortical preactivation level, as reflected by the VEP amplitude in the first block of averages, and habituation was stronger in CC than in CT or TT. The MTHFR C677T polymorphism could thus have an ambiguous role in migraine. On one hand, the better VEP habituation which is associated with its homozygosity, and possibly mediated by homocysteine derivatives increasing serotoninergic transmission, may protect the brain against overstimulation. On the other hand, MTHFR C677T homozygosity is linked to a reduction of grand average VEP amplitude with illness duration, which has been attributed to brain damage. [PubMed Citation] [Order full text from Infotrieve]

17) Cupini LM, Stipa E

## Migraine aura status and hyperhomocysteinaemia.

Cephalalgia. 2007 Jul;27(7):847-9.
[PubMed Citation] [Order full text from Infotrieve]

18) de Tommaso M, Difruscolo O, Sardaro M, Losito L, Serpino C, Pietrapertosa A, Santeramo MT, Dicuonzo F, Carella A, Lamberti P, Livrea P

**Influence of MTHFR genotype on contingent negative variation and MRI abnormalities in migraine.**

Headache. 2007 Feb;47(2):253-65.
[PubMed Citation] [Order full text from Infotrieve]

19) Bottini F, Celle ME, Calevo MG, Amato S, Minniti G, Montaldi L, Di Pasquale D, Cerone R, Veneselli E, Molinari AC

**Metabolic and genetic risk factors for migraine in children.**

Cephalalgia. 2006 Jun;26(6):731-7.
Migraine can induce ischaemic stroke, and is considered an independent risk factor for stroke in the young. To date, the nature of the link between migraine and stroke is essentially unknown. Forty-five children were studied. Homocysteine levels (fasting and post methionine load), vitamin B12 and plasma folate levels, factor V Leiden, factor II G20210A, methylenetetrahydrofolate reductase (MTHFR) C677T and A1298C mutations were examined. Compared with controls, patients with migraine had higher levels of post-methionine load homocysteine values (19.5 +/- 4.9 vs. 16.9 +/- 1.9; P = 0.025) and significantly lower folate levels (5.8 +/- 2.6 vs. 7.5 +/- 2.1; P = 0.002). We found a trend toward an increased risk of migraine in subjects carrying a homozygous mutant genotype for MTHFR C677T and MTHFR A1298C polymorphisms. Genetic prothrombotic conditions do not seem to be related to migraine in the young, whereas the biochemical differences between migrainous patients and controls are an appealing topic for further investigation. [PubMed Citation] [Order full text from Infotrieve]

20) Scher AI, Terwindt GM, Verschuren WM, Kruit MC, Blom HJ, Kowa H, Frants RR, van den Maagdenberg AM, van Buchem M, Ferrari MD, Launer LJ

**Migraine and MTHFR C677T genotype in a population-based sample.**

Ann Neurol. 2006 Feb;59(2):372-5.
[PubMed Citation] [Order full text from Infotrieve]