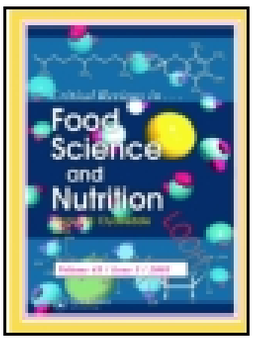

Critical Reviews in Food Science and Nutrition

ISSN: 1040-8398 (Print) 1549-7852 (Online) Journal homepage: http://www.tandfonline.com/loi/bfsn20

Genetic bases of the nutritional approach to migraine

Maria Laura De Marchis, Fiorella Guadagni, Erica Silvestris, Domenica Lovero, David Della-Morte, Patrizia Ferroni, Piero Barbanti & Raffaele Palmirotta

To cite this article: Maria Laura De Marchis, Fiorella Guadagni, Erica Silvestris, Domenica Lovero, David Della-Morte, Patrizia Ferroni, Piero Barbanti & Raffaele Palmirotta (2018): Genetic bases of the nutritional approach to migraine, Critical Reviews in Food Science and Nutrition, DOI: 10.1080/10408398.2018.1450215

To link to this article: https://doi.org/10.1080/10408398.2018.1450215

Accepted author version posted online: 08 Mar 2018.
Published online: 03 Apr 2018.

CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION
https://doi.org/10.1080/10408398.2018.1450215

Taylor & Francis
Taylor & Francis Group

Genetic bases of the nutritional approach to migraine

Maria Laura De Marchis[a,b], Fiorella Guadagni[a,c], Erica Silvestris[d], Domenica Lovero[d], David Della-Morte[c,e], Patrizia Ferroni [a,c], Piero Barbanti[f], and Raffaele Palmirotta [d]

[a]Biobanca Interlstituzionale Multidisciplinare, IRCCS San Raffaele Pisana, Rome, Italy; [b]Biotechnology Unit, Istituto Zooprofilattico Sperimentale del Lazio e della Toscana 'M. Aleandri', Rome, Italy; [c]Department of Human Sciences and Quality of Life Promotion, San Raffaele Roma Open University, Rome, Italy; [d]Department of Biomedical Sciences & Human Oncology, University of Bari 'Aldo Moro', Bari, Italy; [e]Department of Systems Medicine University of Rome "Tor Vergata", Rome, Italy; [f]Headache and Pain Unit, Department of Neurological, Motor and Sensorial Sciences, IRCCS San Raffaele Pisana, Rome, Italy

ABSTRACT

Migraine is a common multifactorial and polygenic neurological disabling disorder characterized by a genetic background and associated to environmental, hormonal and food stimulations. A large series of evidence suggest a strong correlation between nutrition and migraine and indicates several commonly foods, food additives and beverages that may be involved in the mechanisms triggering the headache attack in migraine-susceptible persons. There are foods and drinks, or ingredients of the same, that can trigger the migraine crisis as well as some foods play a protective function depending on the specific genetic sensitivity of the subject. The recent biotechnological advances have enhanced the identification of some genetic factors involved in onset diseases and the identification of sequence variants of genes responsible for the individual sensitivity to migraine trigger-foods. Therefore many studies are aimed at the analysis of polymorphisms of genes coding for the enzymes involved in the metabolism of food factors in order to clarify the different ways in which people respond to foods based on their genetic constitution.

This review discusses the latest knowledge and scientific evidence of the role of gene variants and nutrients, food additives and nutraceuticals interactions in migraine.

KEYWORDS

Migraine; molecular genetics; genes; ppolymorphisms; nutrigenetics; nutrigenomics

Introduction

Migraine is a multifactorial disease, characterized by a complex phenotypic spectrum of clinical manifestations. Hereditary migraine forms [namely, type 1, 2 and 3 Familial Hemiplegic Migraine (FHM)] have been characterized, which are caused by specific mutations in CACNA1A, ATP1A2 and SCN1A genes. Nonetheless, the most common sporadic cases can be attributed also to the concerted effects of genes, lifestyle habits and environmental factors (Burstein, Noseda, and Borsook 2015). Many efforts have been made to identify the genetic loci of susceptibility to various forms of migraine and to interpret the dietary requirements according to specific individual genetic profile(s) (Palmirotta et al. 2013; Silberstein and Dodick 2013).

Based on different methodological approaches, two new disciplines, the nutrigenetics and nutrigenomics have been originated. Nutrigenetics evaluates as individual genetic variations (e.g. polymorphisms or acquired mutations) may influence the response to a specific dietary factor, while nutrigenomics examines how the body reacts to a specific nutritional stimulus through the aid of integrated methods of analysis known as "omic" technologies (Fenech et al. 2011).

Recent studies have reported that diet intervention might complement the pharmacologic treatment of migraine. Accordingly, deeper knowledge of the interaction(s) occurring between nutrients and patients genetic profile could help to develop customized "food therapies", contributing to the improvement of migraineurs' quality of life (Orr 2016).

In this review we considered some foods, additives and nutraceuticals classified as migraine "trigger" (SULT1 inhibitors, alcoholic drinks, histamine and glutamate) or "pain-safe" (magnesium, B vitamin, riboflavin, antioxidant, capsaicin, caffeine), in order to elucidate how the genetic profile may possibly relate to their mechanism of action, thus providing a rationale for future nutrigenetics studies in the field of migraine.

"TRIGGER" Foods for migraine

The genetics of sulfotransferase inhibitors

Several evidences correlate migraine attacks to the consumption of "trigger" foods such as wine, citrus fruits, cheese, coffee and chocolate. All these products contain phenols and polyphenols that, at a biochemical level, act as inhibitors of the sulfotransferase enzymes (Figure 1) (Eagle 2012; Peatfield 1995).

Sulfotransferases (SULT) are a family of enzymes involved in the conjugation of sulfates (SO_{3-2}) to an acceptor alcohol or

CONTACT Raffaele Palmirotta, MD, PhD raffaelepalmirotta@gmail.com Department of Biomedical Sciences and Clinical Oncology, Bari, University of Bari 'Aldo Moro'. P.za Giulio Cesare, 11–70124, Italy.

Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/bfsn.

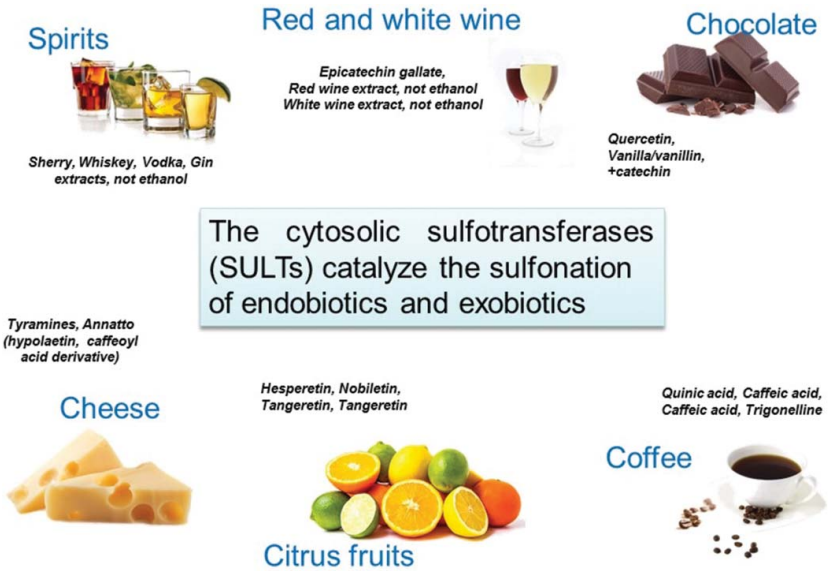

Figure 1. Schematic representation of the main foods and corresponding derivatives able to act as sulfotransferases inhibitors.

amine groups of xenobiotics. The most common biological sulfo acceptor group is 3′-phosphoadenosine-5′-phosphate (PAP), whose conversion leads to the formation of 3′-phosphoadenosine-5′-phosphosulfate (PAPS), critical for the formation of cysteine in cells (Mueller et al. 2015).

Sulfotransferases are a family of enzymes involved in the conjugation of sulfates (SO_{3-2}) to an acceptor alcohol or amine groups to form sulphuric acid esters from various neurotransmitters, proteins, carbohydrates, hormones as well as xenobiotics and their metabolites (Figure 2).

There are five families of sulfotransferase enzymes, classified according to their reaction substrate. In particular, the SULT1 family catalyses the sulfonation of phenolic compounds and catecholamines (SULT1A), thyroid hormones (SULT1B), xenobiotics (SULT1C) and steroidal oestrogens (SULT1E) (Eagle 2012; Mueller et al. 2015). In particular, SULT1A1 and SULT1A3 are responsible for the *in vivo* deactivation of dopamine – whose role in migraine attacks is commonly recognized – and SULT1A inhibition is followed by increased levels of this catecholamine, through the reduction of enzymatic activity (Noseda, Borsook, and Burstein 2017).

Many polymorphisms influencing the activity of the SULT1A gene have been identified. The genetic variant G638A (Arg213His) is associated with the formation of two allozymes, defined as variants *1 (Arg213) and *2 (His213) and characterized by different levels of expression and activity. Individuals homozygous for SULT1A1*2 genotype (His213/His213) show a significantly reduced sulfoniltransferasic platelet activity (Raftogianis et al. 1997). A further variant has been defined as SULT1A1*3, corresponding to the nucleotide conversion A667G (Met223Val), and is characterized by an intermediate activity with respect to variants *1 and *2. Allele frequencies for these polymorphisms differ among populations, showing a greater spread of the allele SULT1A1*1 in Chinese individuals (91.4%), followed by white individuals (65.6%) and African Americans (47.7%) (Nagar, Walther, and Blanchard 2006). Strikingly, a significant reduction in the activity of SULT1A in individuals with migraine has been demonstrated (Littlewood et al. 1982).

The uncommon variant Lys234Asn of the SULT1A3 gene results in the synthesis of a protein more susceptible to proteasome-mediated degradation with a consequent increase in catecholamines levels. This polymorphism has been exclusively identified in people of African American ethnicity (4.2%), which are more prone to develop migraine in adulthood with respect to Asians and Whites (Thomae et al. 2003).

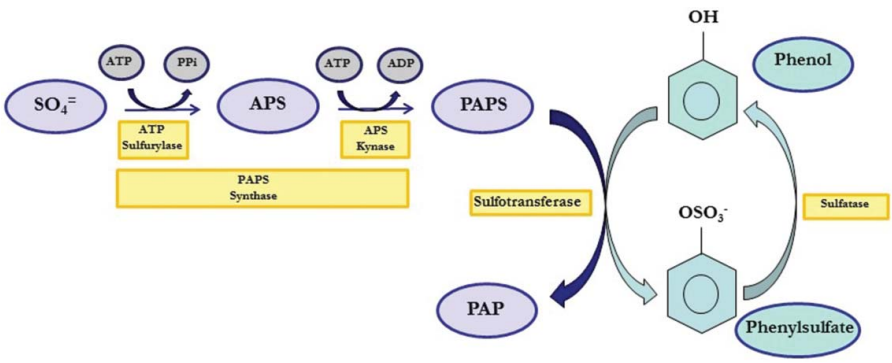

Figure 2. Human sulfation pathway. The process of sulfonation is critical for the metabolism of many chemical substances. APS: adenosine-5 -phosphosulfate; PAPS: 3-phospho-adenosine-5-phosphosulfate; PAP: 3-phosphoadenosine-5-phosphate.

The intake of alcoholic beverages in migraine patients and genetic variants of alcohol dehydrogenase (ADH)

Since antiquity the alcohol intake is known to be a trigger for migraine. Probably, the earliest reference to alcohol-provoked migraine goes back to the writings of Celsius (25 B.C.–50 A.D.) who stated "the pain… is contracted….by drinking wine" and more than six centuries later Paul of Aegina (625–690 A.D.) also included drinking of wine as the triggering factors of migraine (Clifford 1997).

In the classification of the International Headache Society (IHS), two types of alcohol-induced headache were reported among secondary headaches: the immediate alcohol-induced headache, which develops within 3 hours after ingestion of alcoholic beverages, and the delayed alcohol-induced headache, which develops after the blood alcohol level declines or reduces to zero (Society 2004). Many studies in different countries showed that alcohol is a headache trigger in a high percentage of migraine subjects, both in the general (Zivadinov et al. 2003) and headache clinic population (Scharff, Turk, and Marcus 1995). In any case, the opinion of the authors on this issue is very controversial, since many of the retrospective studies are based on subjective information provided by patients, who consider alcohol as the actual trigger of the attacks in only 10% of cases, while the few prospective studies available on this subject are often limited by the low alcohol consumption reported by migraine patients compared to healthy controls (Garcia-Martin et al. 2010a).

There are two alternative hypotheses on how the intake of alcohol could trigger the migraine attack. The first one suggests that alcohol stimulates distinct neuronal circuits converging into the fibres of the trigeminal nerve, resulting in the release of vasoactive and algesic mediators that would activate, in turn, meningeal nociceptors. According to a different hypothesis these receptors would be directly activated by vasodilator, inflammatory or serotonergic mechanisms (Panconesi et al. 2012). Another point of discussion is whether the ethanol itself can constitute the active component in the mechanism of pathogenesis, considering the contribution of other substances contained in alcoholic beverages, such as histamine and phenols flavonoids (Krymchantowski and da Cunha Jevoux 2014). Among the direct effects exercised on the organism by alcohol, the vasodilator action due to the release of calcitonin gene-related peptide (CGRP) by periarterial nerve endings can be easily correlated to the pathogenesis of migraine (Gazzieri et al. 2006).

The involvement of genetic factors in alcohol-provoked migraine has been highlighted by some studies investigating the polymorphisms of the alcohol dehydrogenase (ADH) gene, a major player in the catabolic pathway of ethanol. ADH enzymes are coded by seven genes located on chromosome 4q23. However, only ADH1B, ADH2 and ADH3 loci contain genetic variants with a verified functional impact. In particular, a correlation between alcohol abuse and alcoholism and the SNP rs1229984 (Arg48His), located on the third exon of ADH2 gene, has been established in different populations. More specifically, the allelic variant ADH2*2 (His) seems to play a protective role against alcohol abuse and alcoholism in Asians and Caucasians (Eriksson et al. 2001). As a matter of fact, genotypic and allelic frequencies of this polymorphism were analysed in 197 migraine patients and 255 healthy controls, showing that the His variant was significantly less frequent in migraineurs, regardless of the age of onset of migraine attacks, family history and the presence of aura. Remarkably, the frequency of the His allele has proved to be higher in patients who reported alcohol as a trigger for the attacks, establishing a direct correlation between alcohol intake and genetics in the eziology of alcohol-induced migraine headache (Garcia-Martin et al. 2010a).

Genetic defects in the metabolism of histamine and predisposition to migraine

Histamine (or 2- (4-imidazolyl ethylamine) is an organic molecule belonging to the class of biogenic amines, one of the chemical mediators of inflammation and derives from the pyridoxal phosphate (vitamin B-6) containing L-histidine decarboxylase (HDC) from the amino acid histidine (Bodmer, Imark, and Kneubuhl 1999; Dale and Laidlaw 1910).

It is synthesized and stored in specialized cells such as basophilic granulocytes, platelets, mast cells, interspersed in the connective tissue around the blood vessels in the skin and mucous membranes of the digestive and respiratory tract, histaminergic neurons and entero-chromaffine cells. The intake of certain foods such as milk, fruit, alcohol and chocolate, and drugs can induce the production of histamine by the organism itself. Also in food the production of histamine can be stimulated by storage, processing or bacterial contamination (Bodmer, Imark, and Kneubuhl 1999).

Histamine exerts its effects by binding to one of its 4 receptors (H1R, H2R, H3R, and H4R) on target cells in various tissues, inducing vasoconstriction of the large arteries by action on smooth muscle and vasodilatation of the arterioles for opening of the precapillary sphincters with subsequent alterations of blood pressure and arrhythmias, increasing vascular permeability and mucus secretion, tachycardia, and stimulating gastric acid secretion and nociceptive nerve fibers (Garcia-Martin et al. 2008).

The activity of this amine is involved in the pathogenesis of migraine in several ways. As a matter of fact, a higher frequency of individuals with migraine disorder among patients suffering from allergic diseases has been observed (Wilson et al. 1980). In addition, an increase of plasma histamine, as well as of its amino acid precursor histidine and a spontaneous release of histamine by leukocytes during attacks, have been observed in migraine patients (Garcia-Martin et al. 2008).

Two enzymes are involved in the catabolic pathway of histamine: histamine N-methyl transferase (HNMT), which inactivates histamine in the brain, and the diamine oxidase (DAO), which removes histamine from the extracellular space after its release. Since an impaired activity of these two enzymes could be related to the inability to neutralize the excess of histamine in the body, resulting in a migraine attack, the effects of different functional polymorphisms on the respective coding loci, were tested (Garcia-Martin et al. 2015).

The Thr105Ile variant of HNMT gene, is responsible for a decrease of enzyme activity and shows a frequency of about 10% among Caucasian individuals (Preuss et al. 1998). The

allelic and genotypic frequencies of this polymorphism were analysed in 197 migraine patients and 245 controls, but did not differ significantly between the two groups, nor were related to the age of onset of migraine attacks, sex, personal history of allergic manifestations, family history of migraine or the presence of aura (Garcia-Martin et al. 2008).

Three non-synonymous SNPs called rs10156191 (Thr16Met), rs1049742 (Ser332Phe), and rs1049793 (His645Asp) of the gene coding for the DAO enzyme and a SNP located in the promoter region (rs2052129) were identified and functionally characterized in Caucasian individuals. In particular minor allelic variants of polymorphisms rs1049793, rs10156191 and rs2052129 were associated with a low serum activity of DAO (Maintz et al. 2011). A recent study confirmed that the T allele of rs10156191, which reduces the ability of the enzyme to metabolize circulating histamine, is significantly associated with the risk of developing migraine, especially in women (Garcia-Martin et al. 2015).

These results highlight the importance of investigating in future studies whether migraine patients genetically predisposed to lower levels of DAO enzyme might gain additional benefit from the prescription of a diet low in histamine foods.

Genes involved in glutamate metabolism and predisposition to migraine

Glutamate, a common food additive, is a key excitatory neurotransmitter in the central nervous system. This molecule activates the G protein-coupled metabotropic and ionotropic receptors of kainate, NMDA (N-methyl-D-aspartate) and AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid). The ionotropic AMPA receptor consists of four subunits (GluR1-GluR4) encoded by the genes GRIA1, GRIA2, GRIA3 and GRIA4, respectively. A significant association has been shown between migraine and two polymorphisms located in the first "linkage disequilibrium" block of GRIA1 gene, including its regulatory region and the first two exons. In particular, the T allele of the variant -2012 C/T (rs548294), located on the promoter region, has been associated to the female sex and the subgroup of patients with aura. Conversely, the polymorphisms of genes GRIA2 and GRIA4 so far considered did not show any correlation with the pathogenesis of migraine (Formicola et al. 2010).

Proton magnetic resonance spectroscopy analysis showed a significant reduction of N-acetyl-aspartate and glutamate in superior cerebellar vermis of patients with FHM type 1, and an increase in glutamate/creatinine and glutamate/glutamine ratios in the occipital cortex of female patients, independently of aura (Gonzalez de la Aleja et al. 2013). These data make the genes involved in the synthesis, metabolism and regulation of glutamate and its receptors, potential candidates to the pathogenic mechanisms of migraine. A first genetic evidence derives from a case report about a patient with episodes of ataxia, seizures, migraine and alternating hemiplegia. This man presented a heterozygous mutation in the SLC1A3 gene, not found in his asymptomatic relatives and healthy controls. The SLC1A3 gene codes for the Excitatory Amino Acid Transporter 1 (EAAT1), a glial glutamate transporter (also known as GLAST), mainly expressed in the caudal portion of brainstem and cerebellum, which plays a key role in the removal of glutamate from synapses (Banner et al. 2002). The collected data indicated an alteration of this mechanism as the probable origin of neuronal hyperexcitability, manifesting through the epileptiform discharges and the lowering of the seizure threshold (Jen et al. 2005).

In a subsequent genome wide association (GWA) study, focused on glutamate metabolism and migraine, a correlation between the minor allelic variant A of the marker rs1835740 and migraine susceptibility was found. Two SNPs in "linkage disequilibrium" with the rs1835740 (rs982502 and rs2436046) showed a further association with the disease. The result was more significant in the subgroup of patients with aura (Anttila et al. 2010). The rs1835740 SNP is located on chromosome 8q22.1, between two genes potentially involved in the homeostasis of glutamate: the MTDH/AEG-1 (methaderin/astrocyte-elevated gene-1) and PGCP (plasma glutamate carboxypeptidase) (Anttila et al. 2010). Molecular tests highlighted a correlation between the A variant of the polymorphism and higher transcription levels for the MTDH/AEG1 gene, demonstrating a likely *cis*-regulatory effect of rs1835740 on the synthesis of the transcript. In turn MTDH is known to regulate the SLC1A2 gene, which codes for another member of the family of glutamate transporters (EAAT2). The latter was also investigated for a genetic association with headache, due to the role played by glutamate in the mechanism of migraine chronicization (Shin et al. 2011). The analysis, performed on 74 patients with episodic attacks of headache and 59 chronic patients, showed a significant propensity to drug abuse of patients carrying the A allele of the nucleotide variant A/C of SLC1A2, a factor that predisposes to the transition from episodic to chronic daily headache. Although there is not a direct evidence, the resulting excess of glutamate in the synaptic cleft could be the cause of migraine attacks, due to a drop in the levels of EAAT2 and, presumably, to an increase in the PGCP activity (Shin et al. 2011).

Another positive association was found for the SNP rs1972860 of the gene coding for the ionotropic delta 2 glutamate receptor (GRID2). This locus is located on the 4q22 chromosomal region, previously related to migraine pathophysiology. Sintas et al. tried to replicate the results obtained from Anttila et al. on SNP rs1835740 in a Spanish cohort of 1521 patients and 1379 controls without finding any positive association (Sintas et al. 2012). On the contrary, a GWAS performed on a Swedish population in 2014 confirmed the correlation between migraine and the minor allele of rs1835740 (Ran et al. 2014).

In 2011 the results of a GWA population study, performed of 5122 migraine patients and 18108 healthy controls, highlighted the association between migraine susceptibility and three markers (rs2651899, rs10166942 and rs11172113) located on PRDM16, TRM8 and LRP1 genes, respectively (Chasman et al. 2011). This last gene is of particular interest because its protein is expressed in the brain and vessels, where it modulates synaptic transmission. As a member of the family of lipoprotein receptors, LRP1 works as a sensor of the extracellular environment. This protein also co-localizes and interacts with glutamate receptors (NMDA) confirming previous GWA studies and supporting the prevailing theory of the glutamatergic neurotransmission pathways typical of migraine (Dale and Laidlaw 1910).

"PAIN-SAFE" Foods for migraine

Magnesium metabolism and genetic variants of the estrogen receptor α

Magnesium (Mg^{2+}) is an essential element involved in several biochemical and physiological processes related to the pathogenesis of migraine, which could be classified as a "pain-safe" factor in relation to this disorder.

This chemical element controls the inhibition of neuroinflammatory mechanisms, calcium channels and methyl-D-aspartic acid (NMDA) receptors activity, biosynthesis of nitric oxide and glutamate, and the asset of endogenous hormones (Taylor 2011).

A decrease in Mg^{2+} levels was related to neurogenic inflammation, alteration of mitochondrial permeability, cortical spreading depression (CSD) and increased platelet aggregation (Seelig, and Altura, and Altura 2004).

The possible association between an imbalance in magnesium availability and susceptibility to migraine has been established by two therapeutic trials based on magnesium supplementation (Gaul et al. 2015; Teigen and Boes 2015). Moreover, the concentration of extracellular Mg^{2+} has been related to specific genetic variants of some genes involved in its homeostasis, coding for receptors (CASR: the first to be identified for the common polymorphisms IVS5–89 T> C and A986S), transport proteins (CLDN16, TRPM6, SLC12A3, MRS2, NIPA2, MMgT1, ACDP2 and SLC41A1), regulatory proteins (PHB2, FXYD2, RACK1 and ERK1/2), hormones (oestrogen), and cytokines (EGF) (Shuen et al. 2009). In particular, an association between variants *PvuII* and *XbaI* of the oestrogen receptor α (ESR1) gene and migraine pathology has been reported, although authors have reached discordant results. ESR1 is expressed in the brain where its transcript is regulated by alternative splicing mechanisms that generate distinct protein isoforms in the different neuronal cell types. ESR1 quickly affects neuronal excitability through changes in calcium currents and nitric oxide synthase activation (Colson et al. 2006; Kaunisto et al. 2006). Of interest, Colson et al. showed a significant correlation between the 594A allele of the rs2228480 (G594A) SNP and migraine in two independent case/control groups of Caucasian patients (Colson et al. 2004), but this finding was not confirmed in a study by Kaunisto et al. performed in a larger Finnish cohort of 1,798 individuals (Kaunisto et al. 2006). Similarly, Oterino et al. showed a correlation between the C allele of G325C variant of the ESR1 gene and migraine susceptibility on a Spanish cohort (Oterino et al. 2006), which was not replicated by two independent studies on both Spanish and Australian patients (Colson et al. 2006; Corominas et al. 2009). More recently, Joshi et al. evaluated the same marker on a North Indian population consisting of 217 migraine patients, 217 healthy controls and 179 patients with tension-type headache, showing that the G325C polymorphism was not associated with migraine susceptibility, while the TT genotype and T allele of the *PvuII* variant were significantly associated with female sex and a higher risk of developing migraine with aura (MwA) (Joshi, Pradhan, and Mittal 2010). However, a later study by the same group investigated a set of genes involved in the oestrogen pathway, including ESR1, and a significant correlation with migraine was found only for a specific haplotype comprising the SNPs *PvuII* and *XbaI* (Ghosh et al. 2012). All these studies were incorporated into a recent meta-analysis showing that the ESR1 gene polymorphisms mainly contributing to migraine susceptibility were G594A and C325G, with a more marked effect in Caucasians and a significant association with aura (Li et al. 2015).

Finally, a recent GWAS performed by Rodriguez-Acevedo and collaborators on a genetically isolated population of the Norfolk islands characterized by a high prevalence of migraine, provided further evidence on an effective association between ESR1 and migraine. The analysis, performed on 143 markers, showed a positive association between migraine and ten polymorphisms of ESR1. Six of these SNPs where located in the promoter region of the gene and resulted as part of a single haplotype, suggesting a regulatory role exerted by these variants on the expression levels of ESR1 transcripts (Rodriguez-Acevedo et al. 2013).

At last, these authors re-investigated the G594A and C325G polymorphisms in a selected population of patients affected by pure menstrual and menstrual-related migraine, without showing any significant association. Therefore, according to these results, they hypothesized that G594A and C325G did not play a functional role in the metabolic changes triggering these specific subtypes of migraine (Rodriguez-Acevedo et al. 2014).

The contribution of B vitamins to migraine treatment and genes involved in homocysteine metabolism

Hyperhomocysteinemia is a metabolic disorder affecting epigenetic regulation through disturbance of methylation and related to a major risk of developing migraine. This pathological condition has proven, indeed, to activate trigeminal fibres, inducing meningeal inflammation together with the expansion of cerebral vessels, and causing the typical symptoms of MwA (Lippi et al. 2014).

Levels of circulating plasma homocysteine are influenced by several factors (Figure 3). A major role is played by the dietary availability of folic acid and vitamins B_6 and B_{12}. Furthermore, an increase in homocysteinemia may depend on the presence of specific variants of genes coding for cystathionine β-synthase (CBS), methylenetetrahydrofolate reductase (MTHFR), methionine synthase (MTR) and methionine synthase reductase (MTRR) (Silaste et al. 2001).

Among these, MTHFR genetic variants have been extensively studied in relation to the pathogenesis of migraine. This gene is located on chromosome 1p36.3 and codes for the enzyme involved in the NADPH-dependent reduction of 5,10-methylenetetrahydrofolate to 5-methylene-tetrahydrofolate, acting as a cofactor for the conversion of homocysteine to methionine (Goyette et al. 1994). The functional polymorphism rs1801133 of MTHFR determines the nucleotide substitution C677T, corresponding to the conversion of an alanine residue into valine and resulting into a change of the quaternary structure of the enzyme at its active site. The TT genotype halves the activity of the enzyme, causing a mild hyperhomocysteinemia and this effect is aggravated by the combination with low folate levels (Geisel et al. 2001; Palmirotta et al. 2017).

Several case-control genetic association studies have been performed, looking for a possible correlation between this polymorphism of MTHFR and the increased risk of developing migraine. Rubino et al. transferred the total results into a large

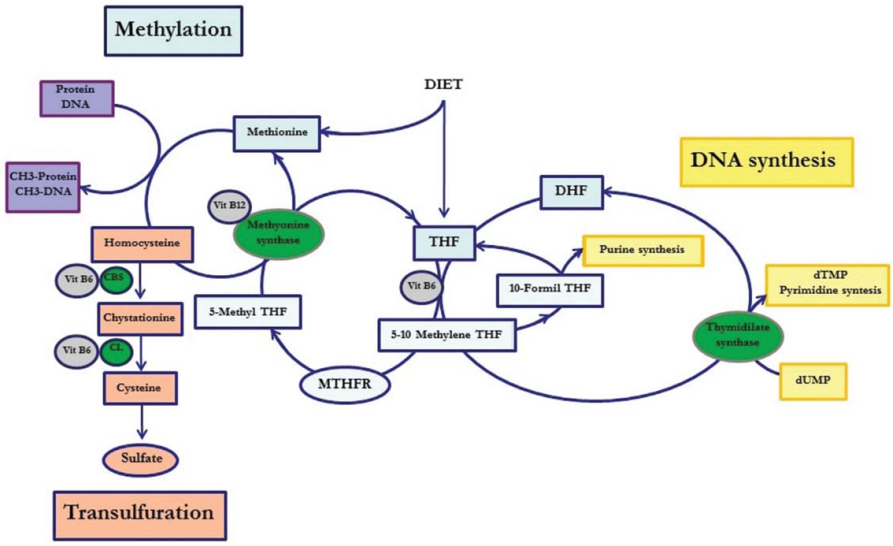

Figure 3. Metabolism of Homocysteine. Folic acid cycle involves recycling of homocysteine to methionine and contains the MTHFR necessary for the formation of 5 Methyl THF. The cystathionine-beta synthase pathway allows the formation of cysteine from homocysteine, that is a precursor of glutathione and hypotaurine. Impaired methylation will lead to genetic numerous major health problems.DHF: Dihydrofolate reductase, THF: Tetrahydrofolate, MTHFR: Methylene Tetrahydrofolate Reductase, CBS: Cystathionine-beta synthase, Cystathionine lyase.

meta-analysis, performed on a total of 2961 migraine patients. Overall, they showed a lack of association between the C677T and susceptibility to migraine, while reporting, at the same time, an increased risk of developing MwA for the subgroups of patients carriers of the TT genotype compared with the other carriers of the CC genotype. Accordingly, the authors hypothesized that hyperhomocysteinemia may sensitize the dura mater and cerebral arteries, promoting the pathogenesis of MwA (Rubino et al. 2009).

Even if this meta-analysis was confirmed by a study performed on a cohort of 267 Caucasian migraine patients, which revealed that individuals carrying the T allele were more likely to develop MwA, contrasting results were collected from a study performed on 25001 women showing the opposite result (Liu et al. 2010; Schurks et al. 2008). Thus, the role of MTHFR on migraine susceptibility is still controversial.

Nonetheless, the assumption of an active role played by the enzyme MTHFR in migraine pathogenesis has been recently reinforced by a GWAS performed on a genetically isolated population of 76 migraine patients resident in the Norfolk islands. The results showed that the 3′ untranslated region (rs4846048), the exon 1 (rs2274976) and the three SNPs of the intron 7 (rs6696752) of MTHFR gene significantly associated with migraine (Stuart et al. 2012).

On the other hand, several evidences confirm that supplementing diet with folic acid, vitamin B_6 and B_{12}, can significantly reduce the levels of circulating homocysteine and migraine disability, particularly in MwA patients. Furthermore the response to treatment seemed to be related with the C677T genotype, with the worst response in TT homozygote individuals, in which a higher dose of supplement should be provided (Lea et al. 2004).

Finally, in 2012 the results from another clinical trial, based on the administration of B vitamins (B_6, B_9 and B_{12}) in a population of 206 women affected by MwA, have been reported. The group receiving vitamin supplementation showed a significant decrease in homocysteine levels paralleled by a lower degree of headache severity and disability compared to the placebo group. Stratifying the population according to genotypes, it was possible to observe that the fraction of patients who best responded to vitamin supplement included individuals carrying the C allele of the C677T variant of MTHFR gene and the A allele of the A66G variant of MTRR gene, although the effects of these two polymorphisms were mutually independent (Menon et al. 2012).

Mitochondrial dysfunction and mtDNA genes involved in the response to riboflavin in migraine patients

Morphological, biochemical and genetic evidences adopt the theory that migraine is related to mitochondrial dysfunction. As a matter of fact, some anomalies affecting the number and the structure of mithocondria have been observed in patients with MwA and FHM (Uncini et al. 1995). Moreover, a large number of biochemical studies have highlighted the occurrence of impaired mitochondrial metabolism in migraine patients, characterized by abnormal levels of lactate and pyruvate in blood and cerebrospinal fluid and reduced activity of several mitochondrial enzymes (Sparaco et al. 2006). Finally, an alteration of mitochondria functionality has resulted into high intracellular levels of Ca^{2+}, an excess of free radicals and a decrease of oxidative phosphorylation. All these events can be responsible for an energy drop at neuronal and astrocytic level, triggering the migraine attack (Metea and Newman 2006).

Further evidences of a possible pathogenic relationship between mitochondrial dysfunction and migraine derive from the finding that several therapeutic agents with a positive action on mitochondrial metabolism showed a beneficial effect in the treatment of this disease [30]. Initially, genetic studies addressed the issue of a correlation between migraine pathogenesis and the mutations classically associated to mitochondrial disorders such as MELAS (mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes), Kearns-Sayre syndrome, MERRF (myoclonic epilepsy with ragged-red fibers) and LHON (Leber hereditary

optic neuropathy), but without success (Stuart et al. 2012). Subsequently, Guo et al. found a positive correlation between the presence of the mutation 3243A>G (associated to MELAS syndrome) and a high prevalence of migraine in a northern European population consisting of 57 mutation carriers and 3471 healthy controls (Guo et al. 2016). Other studies allowed the identification of rare mitochondrial mutations associated to an increased risk of developing migraine, such as the A4336G change and two heteroplasmic variants located in the hypervariable regions 1 and 2 of the mtDNA control region (Wang et al. 2004). Recently, two additional studies identified two SNPs of mtDNA (16519C/T and 3010G/A) and a series of POLG gene mutations altering the mitochondrial DNA replication (T851A, N468D, Y831C, G517V, and P163S) that related to the onset of different diseases, including migraine (Woodbridge et al. 2013). Further evidence of a probable pathogenetic relationship between mitochondrial dysfunction and migraine also derives from the effect that some therapeutic agents with positive action on mitochondrial metabolism such as riboflavin have shown in the treatment of this pathology (Boehnke et al. 2004; Markley 2012). Riboflavin, also known as vitamin B_2, is a vitamin found in food (eggs, green vegetables, milk and meat) and used as a dietary supplement to treat its deficency and prevent migraine.

Di Lorenzo et al. tested the correlation between the individual riboflavin status and specific mtDNA haplogroups on 64 migraine patients, showing that individuals carriers of non-H mitochondrial haplotypes were the best responders, regardless of the presence of aura symptoms. A possible explanation may lay in the association between the H haplogroup and an increased activity of complex I of the electron transport chain, one of the main targets of riboflavin (Di Lorenzo et al. 2009).

Other interesting correlations between riboflavin efficacy and genetic background of migraine patients could in the future derive from the analysis of the already treated C677T polymorphism of the MTHFR gene. The treatment with riboflavin induces a significant decrease of homocysteinemia only in individuals homozygous for the T allele (McNulty et al. 2006). In the future, other interesting correlations between the efficacy of riboflavin treatment and genetic background of the migraine patient could arise from the analysis of the over mentioned C677T polymorphism of the MTHFR gene.

Foods and supplements with antioxidant activity and polymorphisms of genes involved in oxidative metabolism in migraine patients

Oxidative stress represents a key event in the pathogenesis of migraine (Ferroni et al. 2017). It represents the result of an imbalance between the production of reactive oxygen species (ROS) and the antioxidant defence mechanisms that protect against the resulting damage to biological materials in general and to DNA in particular (Ferroni et al. 2017). Indeed, the net effect of ROS on biological processes is considered to be mainly negative, via damage to lipids, proteins and DNA. If left unrepaired, DNA damage may lead to mutagenesis and malignant cell transformation. Lipid peroxidation, in turn, causes deformation of cell structures, and this process is associated with anomalies in cell metabolite transport that can affect physiological function (Volinsky and Kinnunen 2013).

To reduce or even avoid ROS-related DNA damage, consumption of anti-oxidant products is proposed as a means of decreasing the burden of DNA repair. In the cerebral cortex, the formation of ROS would be able to activate nociceptive transmission and cortical spreading depression (CSD) during attacks of MwA (Tuncel et al. 2008). In fact, several clinical evidences support the use of flunarizine, coenzyme Q10, riboflavin and Vitamin E as alternative treatments for migraine, thanks to their antioxidant properties (Butun et al. 2015). By the same principle, in the nutritional field the migraine patient could benefit from a diet rich in green leafy vegetables, some fruits (pomegranate, berries) and spices (turmeric), by virtue of their antioxidant action.

Superoxide dismutase enzymes (SOD) are involved in the conversion of the superoxide ion (O_2^-) into oxygen (O_2) and hydrogen peroxide (H_2O_2), representing one of the most effective defence tool against oxidative stress (Saygi et al. 2015) (Figure 4). We recently performed a study on a population of 490 migraine patients and 246 controls, analysing two common polymorphisms rs2234694 and rs4880, corresponding to the A/C nucleotide change at intron 3 of the SOD1 gene and the amino acid variant Ala16Val (C/T) of the SOD2 gene,

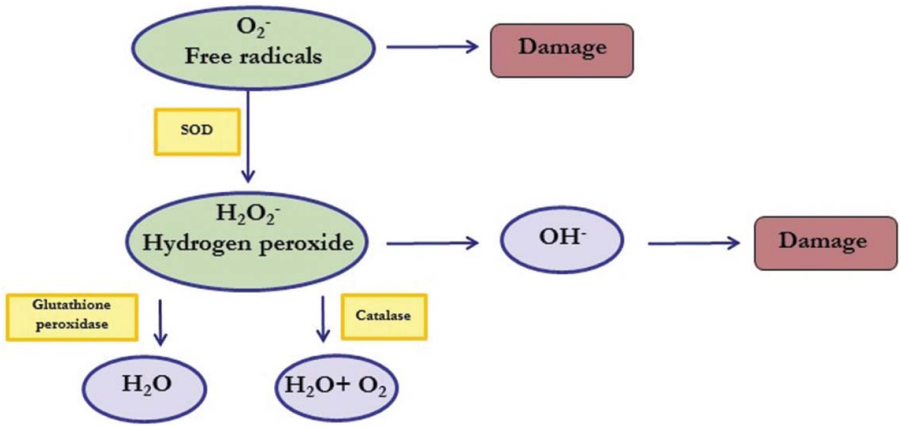

Figure 4. The formation of reactive oxygen species (ROS). Superoxide dismutase enzymes (SODs) catalyze the dismutation of superoxide (O2-) into oxygen (O2) and hydrogen peroxide (H2O2).

respectively. Both substitutions are responsible for a reduction of the enzyme activity. Strikingly, we found an association between the TT genotype of rs4880 variant and the presence of unilateral cranial autonomic symptoms (UAs) and a correlation between the genotype and the type of pharmacological treatment in patients affected by MwA. These results suggested a possible relationship between an altered activity of mitochondrial SOD2 and a defective control of oxidative phenomena inducing CSD, neurological stimulation in the trigeminal system and UAs triggering (Palmirotta et al. 2015).

These polymorphisms, together with the CAT2 variants -262 C/T and -21 A/T, have been recently genotyped by Saygi et al. in a cohort of 96 migraine paediatric patients, showing a significant difference in the distribution of genotype frequencies of the SOD2 polymorphism 16 C/T and its C allele between migraine patients and healthy controls. In addition, the A/A genotype and A allelic variant of the -21 A/T polymorphism of the catalase gene – coding for another key antioxidant enzyme – were more frequent in migraineurs compared with controls (Saygi et al. 2015).

Also the PON1 gene, that codes for paraoxonase 1 (a serum phosphatase with antioxidant activity involved in the metabolism of organophosphorus compounds and lipids) seems to play a role in the pathogenesis of migraine (Cowan et al. 2001). PON1 activity is under the control of several genetic variants. Among these, SNPs rs854560 (L55M) and rs662 (Q192R) were considered in a study performed on a population of 197 Spanish Caucasian migraine patients, showing no association between allele frequencies and migraine susceptibility. However, patients carriers of the Q allele for the Q192R variant (associated with a higher rate of protein hydrolysis) displayed an early age of migraine episodes onset (Garcia-Martin et al. 2010b). In a subsequent study, the levels of PON1 enzyme activity were investigated by biochemical assays in relation to the risk of developing migraine in a Turkish population consisting of 104 patients with migraine and 86 healthy subjects. The activity of serum PON1 showed a significant decrease in patients with migraine. Also in this case polymorphisms rs854560 and rs662 were genotyped, without finding any significant difference in allele frequencies between patients and controls (Yildirim et al. 2011).

These data are of particular interest for their functional implications on migraine treatment. In fact, starting from these evidences, further studies could be performed to understand the effect of a personalized treatment based on food or supplements with antioxidant properties in those patients who are genetically predisposed to a deficit of the enzymatic systems operating against oxidative stress.

Genetic variants of the trpv1 gene and activity of capsaicin in migraine

Transient receptor potential (TRP) channels are a group of ion channels that transport cations of sodium, calcium and magnesium, which act as mediators of sensory signals (Nilius and Owsianik 2011).

Mammalian TRP channels comprise 28 members that share some structural homology of amino acid sequences to each other and are subclassified in: TRPC (Canonical), TRPV (Vanilloid), TRPM (Melastatin), TRPP (Polycystin), TRPML (Mucolipin) and TRPA (Ankyrin) (Kaneko and Szallasi 2014).

TRP channels are therefore 'cellular sensors' that mediate different sensations like pain, hotness, coldness or different kinds of tastes, determined by physical and chemical stimuli.

Some TRP channels are activated by natural products like garlic (allicin), wasabi (allyl isothiocyanate); menthol, camphor, peppermint, or chilli pepper (capsaicin) (Kaneko and Szallasi 2014) (Figure 5). Capsaicin and several related compounds called capsaicinoids are active components of the chili peppers, which are plants belonging to the genus *Capsicum*. These are irritant and produces a sensation of burning in any tissue with which it comes into contact. (Cianchetti 2010) (Figure 5). Capsaicin compound is an agonist of the TRPV1 and has been found to be effective in the treatment of many categories of neuropathic pain, particularly of post-herpetic type and in the treatment of migraine. The activation of TRPV1 receptor induces the

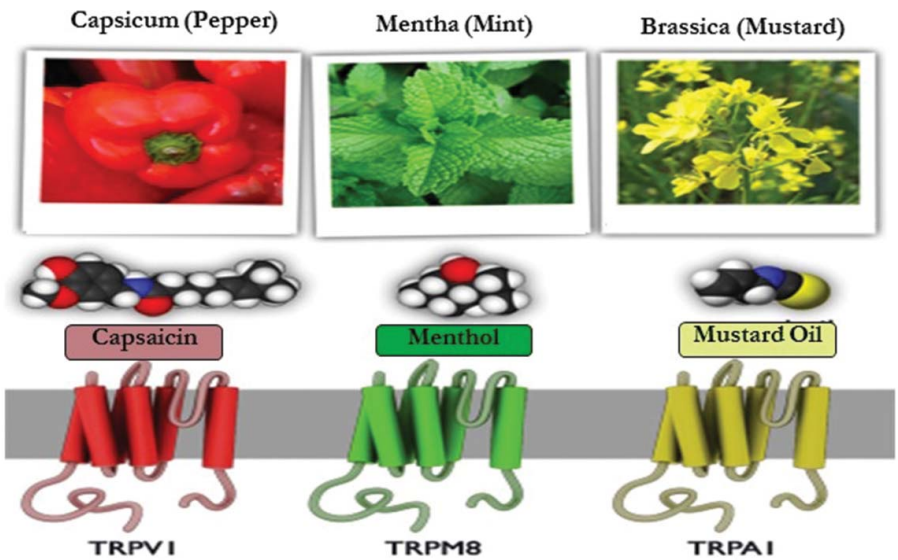

Figure 5. Capsaicin, Menthol and Mustard Oil as agonists of the TRPV1, TRPM8 and TRPAI Receptors.

depolarization of sensory neurons and a refractory state of nociceptive fibres, with the subsequent release of CGRP, substance P and other active neuropeptides. Since the ongoing local exposure to high doses of capsaicin promotes the lowering of pain through the inactivation of nociceptors, dermal patches and capsaicin creams have been developed for the topical treatment of chronic painful neuropathies and migraine (Cianchetti 2010).

In 2012, a genetic case-control study was performed to verify the presence of genetic variants belonging to ten TRP family genes that could be associated to migraine pathogenesis (Carreno et al. 2012). A nominal association with susceptibility to migraine disease was effectively found for the variants rs7217270 (TRPV3) and rs222741 (TRPV1). However, it is still not clear whether these variants have a functional significance or are in "*linkage disequilibrium*" with other migraine susceptibility loci (Carreno et al. 2012).

Further studies should be performed to test the effect of these SNPs on the response to capsaicin treatment in order to evaluate a possible stratification of patients in therapeutic treatment.

Correlation between anti-migraine effect of caffeine and polymorphisms of A2AR Adenosine Receptor

Caffeine is a central nervous system (CNS) stimulant of the methylxanthine alkaloid class chemically related to the adenine

Table 1. Reported association studies between migraine foods, additives and nutraceuticals gene polymorphisms classified as migraine "trigger" or "pain-safe".

Effect on migraine	Foods, additives and nutraceuticals	Gene	PolymorphismS	References
"trigger"	SULT1 inhibitors	SULT1A1	G638A (Arg213His)	Raftogianis et al. 1997
			A667G (Met223Val)	Nagar, Walther, and Blanchard 2006; Littlewood et al. 1982
		SULT1A3	Lys234Asn	Thomae et al. 2003
	Alcoholic drinks	ADH2	rs1229984 (Arg48His)	Eriksson et al. 2001; Garcia-Martin et al. 2010a
	Histamine	HNMT	Thr105Ile	Preuss et al. 1998; Garcia-Martin et al. 2008
		DAO	rs10156191 (Thr16Met), rs1049742 (Ser332Phe), rs1049793 (His645Asp), (rs2052129)	Maintz et al. 2011
			rs10156191	Garcia-Martin et al. 2015
	Glutamate	GRIA1	−2012 C/T (rs548294)	Formicola et al. 2010
		EAAT1/SLC1A3	C1047G	Jen et al. 2005
		Intergenic between MTDH/AEG-1 and PGCP	rs1835740	Anttila et al. 2010; Sintas et al. 2012; Ran et al. 2014
		EAAT2/ SLC1A2	−181A/C	Shin et al. 2011
		GRID2	rs1972860	Ligthart et al. 2011
		PRDM16	rs2651899	Chasman et al. 2011
		TRM8	rs10166942	
		LRP1	rs11172113	
"pain-safe"	Magnesium	ESR1	rs2228480 (G594A)	Colson et al. 2004; Kaunisto et al. 2006
			C325G (rs1801132)	Oterino et al. 2006; Colson et al. 2006; Corominas et al. 2009
			PvuII (rs2234693) C325G (rs1801132) PROGINS (rs1042838)	Joshi, Pradhan, and Mittal 2010
			c454–397T>C *PvuII* (rs2234693) c454–351A>G *XbaI* (rs9340799)	Ghosh et al. 2012; Li et al. 2015
			143 markers	Rodriguez-Acevedo et al. 2013
			G594A and C325G	Rodriguez-Acevedo et al. 2014
	B vitamin	MTHFR	C677T (rs1801133)	Schurks et al. 2008; Rubino et al. 2009; Liu et al. 2010
		MTHFR	rs4846048, rs2274976 and rs6696752	Stuart et al. 2012
		MTHFR	C677T	Menon et al. 2012
		MTRR	A66G	
	Riboflavin	mtDNA	A3243G	Guo et al. 2016
		mtDNA	A4336G	Wang et al. 2004
		mtDNA	C16519T and G3010A	Woodbridge et al. 2013
		POLG	T851A, N468D, Y831C, G517V and P163S	
		mtDNA	H haplogroup	Di Lorenzo et al. 2009
		MTHFR	C677T	McNulty et al. 2006
	Antioxidant	SOD2	rs4880 (C/T) (Ala16Val)	Palmirotta et al. 2015
		CAT2	−262 C/T and -21 A/T	Saygi et al. 2015
		PON1	rs854560 (L55M) and rs662 (Q192R)	Garcia-Martin et al. 2010b; Yildirim et al. 2011
	Capsaicin	TRPV1	rs222741	Carreno et al. 2012
		TRPV3	rs7217270	
	Caffeine	A2AR	rs5751876	Hamilton et al. 2004
			rs5760405, rs5751876, rs35320474, rs5751862, rs3761422 and rs4822492	Hohoff et al. 2007

and guanine bases of DNA and RNA. It is the world's most widely consumed psychoactive drug. In 1993 this substance has been classified as a safe and effective category 1 adjuvant analgesic when taken in combination with paracetamol and acetylsalicylic acid in the treatment of specific types of pain, comprising headache, thanks to the inhibition of the synthesis of prostaglandin E2 in microglial cells (Diener et al. 2005).

There are several known mechanisms of action to explain the effects of caffeine. The most prominent one is a reversible block of the action of adenosine on its receptor. Consequently, the onset of drowsiness induced by adenosine is prevented. Caffeine, in fact, acts as an antagonist of the A2AR receptor (A_{2A} adenosine receptor), whose activity is closely related to the pathophysiology of migraine since it attenuates the inhibitory capacity of the A1 receptors, facilitating the receptor-mediated transmission of NMDA, which favours the genesis of CSD (Lauritzen 1994). In addition, the receptor A2AR modulates the excitatory effects of CGRP by means of synaptic transmission in the hippocampal CA1 area and release of vasoactive intestinal polypeptide (VIP) and γ-aminobutyric acid (GABA) (Sebastiao and Ribeiro 2000). In relation to its mechanism of action it is possible to hypothesize that the A2AR gene variations could affect susceptibility to migraine.

In 2007, Hohoff et al. presented a case-control study performed on 265 patients affected by migraine with or without aura, and 154 controls, analysing three different exonic polymorphisms (rs5760405, rs5751876 and rs35320474) and three variants located in the intronic flanking regions of A2AR gene (rs5751862, rs3761422 and rs4822492). The genotype frequencies of these six polymorphisms were in Hardy-Weinberg equilibrium and in strong "*linkage disequilibrium*". This single haplotype block showed five different combinations with an allelic frequency higher than 1%. Among these alleles, the haplotype GCCCTG was more frequent in MwA patients (12%) compared to the control group (6%) (Hohoff et al. 2007).

An interesting aspect about this finding is that the exon polymorphism rs5751876 was previously associated with panic disorders (Hamilton et al. 2004). Patients suffering from such diseases respond in an adverse manner to caffeine, suggesting that alternative allelic variants of the A2AR gene can modify the risk of developing MwA and panic disorders. On this basis, it would be interesting to investigate whether MwA patients carriers of haplotype GCCCTG could more favourably respond to the effects of caffeine, thus setting the rationale for future studies of nutrigenomics on caffeine and migraine (Hohoff et al. 2007).

Conclusions

It is well established that diet can modulate the physiological functions of an individual, interacting with the metabolic and molecular pathways that regulate all activities in the human body. In the post-genomic era, thanks to the technology and analysis software currently available for the execution of large-scale population studies, the correlations between food and genetics can finally be identified.

The results of case-control association genetic studies are increasingly highlighting the correlations between the molecular pathways regulated by nutrients and the pathogenesis of migraine (Table 1). Clinical evidences supporting the positive or negative effects of certain foods or nutraceuticals in the treatment of the migraine patients are now numerous and consolidated. However, the link between the genetic background of the migraine patient and the response to a personalized nutritional treatment has been established with certainty only for some substances, while in most cases it is still speculative. Undoubtedly non-modifiable factors such as genetic predisposition are associated with modifiable risk factors including coffee abuse, obesity, stressful life events, sleep disturbances, medication overuse, proinflammatory and prothrombotic diseases or low socioeconomic status (Pistoia, Sacco, and Carolei 2013).

Therefore, the next step would be to correlate the knowledge so far obtained in the fields of genetics of migraine and nutrigenetics. This would allow to stratify migraine patients according to their specific genotype and to assess whether, using this approach, the contribution of specific foods or dietary supplements may prove to be effective in the personalized care of this disabling disease.

Disclosure of interests

The authors report no conflicts of interest.

Acknowledgment

The authors would also like to thank Associazione per la Ricerca Biomolecolare Onlus for supporting the publication of this paper.

ORCID

Patrizia Ferroni http://orcid.org/0000-0002-9877-8712
Raffaele Palmirotta http://orcid.org/0000-0002-9401-7377

References

Anttila, V., H. Stefansson, M. Kallela, U. Todt, G. M. Terwindt, M. S. Calafato, D. R. Nyholt, A. S. Dimas, T. Freilinger, B. Muller-Myhsok, et al. 2010. Genome-wide association study of migraine implicates a common susceptibility variant on 8q22.1. *Nature Genetics* 42:869–73.

Banner, S. J., A. E. Fray, P. G. Ince, M. Steward, M. R. Cookson, and P. J. Shaw. 2002. The expression of the glutamate re-uptake transporter excitatory amino acid transporter 1 (EAAT1) in the normal human CNS and in motor neurone disease: an immunohistochemical study. *Neuroscience* 109:27–44.

Bodmer, S., C. Imark, and M. Kneubuhl. 1999. Biogenic amines in foods: histamine and food processing. *Inflammation Research* 48:296–300.

Boehnke, C., U. Reuter, U. Flach, S. Schuh-Hofer, K. M. Einhaupl, and G. Arnold. 2004. High-dose riboflavin treatment is efficacious in migraine prophylaxis: an open study in a tertiary care centre. *European Journal of Neurology* 11:475–77.

Burstein, R., R. Noseda, and D. Borsook. 2015. Migraine: multiple processes, complex pathophysiology. *Journal of Neuroscience* 35:6619–29.

Butun, A., M. Naziroglu, S. Demirci, O. Celik, and A. C. Uguz. 2015. Riboflavin and vitamin E increase brain calcium and antioxidants, and microsomal calcium-ATP-ase values in rat headache models induced by glyceryl trinitrate. *Journal of Membrane Biology* 248:205–13.

Carreno, O., R. Corominas, J. Fernandez-Morales, M. Camina, M. J. Sobrido, J. M. Fernandez-Fernandez, P. Pozo-Rosich, B. Cormand, and A. Macaya. 2012. SNP variants within the vanilloid TRPV1 and TRPV3 receptor genes

are associated with migraine in the Spanish population. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics* 159B:94–103.
Chasman, D. I., M. Schurks, V. Anttila, B. de Vries, U. Schminke, L. J. Launer, G. M. Terwindt, A. M. van den Maagdenberg, K. Fendrich, et al. 2011. Genome-wide association study reveals three susceptibility loci for common migraine in the general population. *Nature Genetics* 43:695–98.
Cianchetti, C. 2010. Capsaicin jelly against migraine pain. *International Journal of Clinical Practice* 64:457–59.
Clifford, R. F. 1997. Food and headache. *Headache* 8:319–29.
Colson, N. J., R. A. Lea, S. Quinlan, and L. R. Griffiths. 2006. No role for estrogen receptor 1 gene intron 1 Pvu II and exon 4 C325G polymorphisms in migraine susceptibility. *Bmc Medical Genetics [Electronic Resource]* 7:12.
Colson, N. J., R. A. Lea, S. Quinlan, J. MacMillan, and L. R. Griffiths. 2004. The estrogen receptor 1 G594A polymorphism is associated with migraine susceptibility in two independent case/control groups. *Neurogenetics* 5:129–33.
Corominas, R., M. Ribases, E. Cuenca-Leon, B. Cormand, and A. Macaya. 2009. Lack of association of hormone receptor polymorphisms with migraine. *European Journal of Neurology* 16:413–15.
Cowan, J., C. M. Sinton, A. W. Varley, F. H. Wians, R. W. Haley, and R. S. Munford. 2001. Gene therapy to prevent organophosphate intoxication. *Toxicology and Applied Pharmacology* 173:1–6.
Dale, H. H., and P. P. Laidlaw. 1910. The physiological action of beta-iminazolylethylamine. *Journal of Physiology* 41:318–44.
Eagle, K. 2012. Toxicological effects of red wine, orange juice, and other dietary SULT1A inhibitors via excess catecholamines. *Food and Chemical Toxicology* 50:2243–49.
Eriksson, C. J., T. Fukunaga, T. Sarkola, W. J. Chen, C. C. Chen, J. M. Ju, A. T. Cheng, H. Yamamoto, K. Kohlenberg-Muller, M. Kimura, et al. 2001. Functional relevance of human adh polymorphism. *Alcoholism, Clinical and Experimental Research* 25:157S–63S.
Fenech, M., A. El-Sohemy, L. Cahill, L. R. Ferguson, T. A. French, E. S. Tai, J. Milner, W. P. Koh, L. Xie, M. Zucker, M. Buckley, et al. 2011. Nutrigenetics and nutrigenomics: viewpoints on the current status and applications in nutrition research and practice. *Journal Nutrigenet Nutrigenomics* 4:69–89.
Ferroni, P., P. Barbanti, D. Della-Morte, R. Palmirotta, E. Jirillo, and F. Guadagni. 2017. Redox Mechanisms in Migraine: Novel Therapeutics and Dietary Interventions. *Antioxid Redox Signal*. Published Online: 21 Nov 2017.
Formicola, D., A. Aloia, S. Sampaolo, O. Farina, D. Diodato, L. R. Griffiths, F. Gianfrancesco, G. Di Iorio, and T. Esposito. 2010. Common variants in the regulative regions of GRIA1 and GRIA3 receptor genes are associated with migraine susceptibility. *BMC Medical Genetics [Electronic Resource]* 11:103.
Garcia-Martin, E., C. Martinez, M. Serrador, H. Alonso-Navarro, P. Ayuso, F. Navacerrada, J. A. Agundez, and F. J. Jimenez-Jimenez. 2015. Diamine oxidase rs10156191 and rs2052129 variants are associated with the risk for migraine. *Headache* 55:276–86.
Garcia-Martin, E., C. Martinez, M. Serrador, H. Alonso-Navarro, F. Navacerrada, J. A. Agundez, and F. J. Jimenez-Jimenez. 2008. Histamine-N-methyl transferase polymorphism and risk for migraine. *Headache* 48:1343–48.
Garcia-Martin, E., C. Martinez, M. Serrador, H. Alonso-Navarro, F. Navacerrada, J. A. Agundez, and F. J. Jimenez-Jimenez. 2010a. Alcohol dehydrogenase 2 genotype and risk for migraine. *Headache* 50:85–91.
Garcia-Martin, E., C. Martinez, M. Serrador, H. Alonso-Navarro, F. Navacerrada, J. A. Agundez, and F. J. Jimenez-Jimenez. 2010b. Paraoxonase 1 (PON1) polymorphisms and risk for migraine. *Journal of Neurology* 257:1482–85.
Gaul, C., H. C. Diener, U. Danesch, and G. Migravent Study. 2015. Improvement of migraine symptoms with a proprietary supplement containing riboflavin, magnesium and Q10: a randomized, placebo-controlled, double-blind, multicenter trial. *Journal Headache Pain* 16:516.
Gazzieri, D., M. Trevisani, F. Tarantini, P. Bechi, G. Masotti, G. F. Gensini, S. Castellani, N. Marchionni, P. Geppetti, and S. Harrison. 2006. Ethanol dilates coronary arteries and increases coronary flow via transient receptor potential vanilloid 1 and calcitonin gene-related peptide. *Cardiovascular Research* 70:589–99.
Geisel, J., I. Zimbelmann, H. Schorr, J. P. Knapp, M. Bodis, U. Hubner, and W. Herrmann. 2001. Genetic defects as important factors for moderate hyperhomocysteinemia. *Clinical Chemistry and Laboratory Medicine* 39:698–704.
Ghosh, J., G. Joshi, S. Pradhan, and B. Mittal. 2012. Potential role of aromatase over estrogen receptor gene polymorphisms in migraine susceptibility: a case control study from North India. *PLOS One* 7: e34828.
Gonzalez de la Aleja, J., A. Ramos, V. Mato-Abad, A. Martinez-Salio, J. A. Hernandez-Tamames, J. A. Molina, J. Hernandez-Gallego, and J. Alvarez-Linera. 2013. Higher glutamate to glutamine ratios in occipital regions in women with migraine during the interictal state. *Headache* 53:365–75.
Goyette, P., J. S. Sumner, R. Milos, A. M. Duncan, D. S. Rosenblatt, R. G. Matthews, and R. Rozen. 1994. Human methylenetetrahydrofolate reductase: isolation of cDNA mapping and mutation identification. *Nature Genetics* 7:551.
Guo, S., A. L. Esserlind, Z. Andersson, A. L. Frederiksen, J. Olesen, J. Vissing, and M. Ashina. 2016. Prevalence of migraine in persons with the 3243A>G mutation in mitochondrial DNA. *European Journal of Neurology* 23:175–81.
Hamilton, S. P., S. L. Slager, A. B. De Leon, G. A. Heiman, D. F. Klein, S. E. Hodge, M. M. Weissman, A. J. Fyer, and J. A. Knowles. 2004. Evidence for genetic linkage between a polymorphism in the adenosine 2A receptor and panic disorder. *Neuropsychopharmacology* 29:558–65.
Hohoff, C., M. Marziniak, K. P. Lesch, J. Deckert, C. Sommer, and R. Mossner. 2007. An adenosine A2A receptor gene haplotype is associated with migraine with aura. *Cephalalgia* 27:177–81.
iener, H. C., V. Pfaffenrath, L. Pageler, H. Peil, and B. Aicher. 2005. The fixed combination of acetylsalicylic acid, paracetamol and caffeine is more effective than single substances and dual combination for the treatment of headache: a multicentre, randomized, double-blind, single-dose, placebo-controlled parallel group study. *Cephalalgia* 25:776–87.
Jen, J. C., J. Wan, T. P. Palos, B. D. Howard, and R. W. Baloh. 2005. Mutation in the glutamate transporter EAAT1 causes episodic ataxia, hemiplegia, and seizures. *Neurology* 65:529–34.
Joshi, G., S. Pradhan, and B. Mittal. 2010. Role of the oestrogen receptor (ESR1 PvuII and ESR1 325 C->G) and progesterone receptor (PROGINS) polymorphisms in genetic susceptibility to migraine in a North Indian population. *Cephalalgia* 30:311–20.
Kaneko, Y., and A. Szallasi. 2014. Transient receptor potential (TRP) channels: a clinical perspective. *British Journal of Pharmacology* 171:2474–507.
Kaunisto, M. A., M. Kallela, E. Hamalainen, R. Kilpikari, H. Havanka, H. Harno, M. Nissila, E. Sako, M. Ilmavirta, J. Liukkonen, et al. 2006. Testing of variants of the MTHFR and ESR1 genes in 1798 Finnish individuals fails to confirm the association with migraine with aura. *Cephalalgia* 26:1462–72.
Krymchantowski, A. V., and C. da Cunha Jevoux. 2014. Wine and headache. *Headache* 54:967–75.
Lauritzen, M. 1994. Pathophysiology of the migraine aura. The spreading depression theory. *Brain* 117 (Pt 1):199–210.
Lea, R. A., M. Ovcaric, J. Sundholm, J. MacMillan, and L. R. Griffiths. 2004. The methylenetetrahydrofolate reductase gene variant C677T influences susceptibility to migraine with aura. *BMC Medicine [Electronic Resource]* 2:3.
Li, L., R. Liu, Z. Dong, X. Wang, and S. Yu. 2015. Impact of ESR1 Gene Polymorphisms on Migraine Susceptibility: A Meta-Analysis. *Medicine* 94:e0976.
Ligthart, L., B. de Vries, A. V. Smith, M. A. Ikram, N. Amin, J. J. Hottenga, S. C. Koelewijn, V. M. Kattenberg, M. H. de Moor, A. C. Janssens, et al. 2011. Meta-analysis of genome-wide association for migraine in six population-based European cohorts. *European Journal of Human Genetics* 19(8):901–07.
Lippi, G., C. Mattiuzzi, T. Meschi, G. Cervellin, and L. Borghi. 2014. Homocysteine and migraine. A narrative review. *Clinica Chimica Acta* 433:5–11.
Littlewood, J., V. Glover, M. Sandler, R. Petty, R. Peatfield, and F. C. Rose. 1982. Platelet phenolsulphotransferase deficiency in dietary migraine. *Lancet* 1:983–86.

Liu, A., S. Menon, N. J. Colson, S. Quinlan, H. Cox, M. Peterson, T. Tiang, L. M. Haupt, R. A. Lea, and L. R. Griffiths. 2010. Analysis of the MTHFR C677T variant with migraine phenotypes. *BMC Res Notes* 3:213.

Lorenzo Di, C., F. Pierelli, G. Coppola, G. S. Grieco, C. Rengo, M. Ciccolella, D. Magis, M. Bolla, C. Casali, F. M. Santorelli, and J. Schoenen. 2009. Mitochondrial DNA haplogroups influence the therapeutic response to riboflavin in migraineurs. *Neurology* 72:1588–94.

Maintz, L., C. F. Yu, E. Rodriguez, H. Baurecht, T. Bieber, T. Illig, S. Weidinger, and N. Novak. 2011. Association of single nucleotide polymorphisms in the diamine oxidase gene with diamine oxidase serum activities. *Allergy* 66:893–902.

Markley, H. G. 2012. CoEnzyme Q10 and riboflavin: the mitochondrial connection. *Headache* 52 (Suppl 2):81–87.

McNulty, H., R. C. Dowey le, J. J. Strain, A. Dunne, M. Ward, A. M. Molloy, L. B. McAnena, J. P. Hughes, M. Hannon-Fletcher, and J. M. Scott. 2006. Riboflavin lowers homocysteine in individuals homozygous for the MTHFR 677C->T polymorphism. *Circulation* 113:74–80.

Menon, S., R. A. Lea, B. Roy, M. Hanna, S. Wee, L. M. Haupt, C. Oliver, and L. R. Griffiths. 2012. Genotypes of the MTHFR C677T and MTRR A66G genes act independently to reduce migraine disability in response to vitamin supplementation. *Pharmacogenet Genomics* 22:741–49.

Metea, M. R., and E. A. Newman. 2006. Glial cells dilate and constrict blood vessels: a mechanism of neurovascular coupling. *Journal of Neuroscience* 26:2862–70.

Mueller, J. W., L. C. Gilligan, J. Idkowiak, W. Arlt, and P. A. Foster. 2015. The Regulation of Steroid Action by Sulfation and Desulfation. *Endocrine Reviews* 36:526–63.

Nagar, S., S. Walther, and R. L. Blanchard. 2006. Sulfotransferase (SULT) 1A1 polymorphic variants *1, *2, and *3 are associated with altered enzymatic activity, cellular phenotype, and protein degradation. *Molecular Pharmacology* 69:2084–92.

Nilius, B., and G. Owsianik. 2011. The transient receptor potential family of ion channels. *Genome Biology* 12:218.

Noseda, R., D. Borsook, and R. Burstein. 2017. Neuropeptides and Neurotransmitters That Modulate Thalamo-Cortical Pathways Relevant to Migraine Headache. *Headache* 57(Suppl 2):97–111.

Orr, S. L. 2016. Diet and nutraceutical interventions for headache management: A review of the evidence. *Cephalalgia* 36:1112–33.

Oterino, A., J. Pascual, C. Ruiz de Alegria, N. Valle, J. Castillo, Y. Bravo, F. Gonzalez, P. Sanchez-Velasco, A. Cayon, F. Leyva-Cobian, et al. 2006. Association of migraine and ESR1 G325C polymorphism. *Neuroreport* 17:61–64.

Palmirotta, R., P. Barbanti, M. L. De Marchis, G. Egeo, C. Aurilia, L. Fofi, C. Ialongo, M. G. Valente, P. Ferroni, and D. Della-Morte, et al. 2015. Is SOD2 Ala16Val polymorphism associated with migraine with aura phenotype. *Antioxid Redox Signal* 22:275–79.

Palmirotta, R., P. Barbanti, G. Ludovici, G. Egeo, C. Aurilia, L. Fofi, M. L. De Marchis, A. Spila, P. Ferroni, D. Della-Morte, et al. 2013. Establishment of a biorepository for migraine research: the experience of Interinstitutional Multidisciplinary BioBank (BioBIM). *Neurological Sciences* 34:1659–63.

Palmirotta, R., D. Lovero, E. Silvestris, V. Simone, L. Lanotte, D. Quaresmini, and F. Silvestris. 2017. Characterization of a Rare Nonpathogenic Methylenetetrahydrofolatereductase (MTHFR) Gene Mutation p.Lys215del in a Southern Italian family. *Human Mutation* 38:120–21.

Panconesi, A., M. L. Bartolozzi, S. Mugnai, and L. Guidi. 2012. Alcohol as a dietary trigger of primary headaches: what triggering site could be compatible. *Neurological Sciences* 33(Suppl 1):S203–205.

Peatfield, R. C. 1995. Relationships between food, wine, and beer-precipitated migrainous headaches. *Headache* 35:355–57.

Pistoia, F., S. Sacco, A. Carolei. 2013. Behavioral therapy for chronic migraine. *Current Pain and Headache Reports* 17(1):304.

Preuss, C. V., T. C. Wood, C. L. Szumlanski, R. B. Raftogianis, D. M. Otterness, B. Girard, M. C. Scott, and R. M. Weinshilboum. 1998. Human histamine N-methyltransferase pharmacogenetics: common genetic polymorphisms that alter activity. *Molecular Pharmacology* 53:708–17.

Raftogianis, R. B., T. C. Wood, D. M. Otterness, J. A. Van Loon, and R. M. Weinshilboum. 1997. Phenol sulfotransferase pharmacogenetics in humans: association of common SULT1A1 alleles with TS PST phenotype. *Biochemical and Biophysical Research Communications* 239:298–304.

Ran, C., L. Graae, P. K. Magnusson, N. L. Pedersen, L. Olson, and A. C. Belin. 2014. A replication study of GWAS findings in migraine identifies association in a Swedish case-control sample. *BMC Medical Genetics [Electronic Resource]* 15:38.

Rodriguez-Acevedo, A. J., B. H. Maher, R. A. Lea, M. Benton, and L. R. Griffiths. 2013. Association of oestrogen-receptor gene (ESR1) polymorphisms with migraine in the large Norfolk Island pedigree. *Cephalalgia* 33:1139–47.

Rodriguez-Acevedo, A. J., R. A. Smith, B. Roy, H. Sutherland, R. A. Lea, A. Frith, E. A. MacGregor, and L. R. Griffiths. 2014. Genetic association and gene expression studies suggest that genetic variants in the SYNE1 and TNF genes are related to menstrual migraine. *J Headache Pain* 15:62.

Rubino, E., M. Ferrero, I. Rainero, E. Binello, G. Vaula, and L. Pinessi. 2009. Association of the C677T polymorphism in the MTHFR gene with migraine: a meta-analysis. *Cephalalgia* 29:818–25.

Saygi, S., I. Erol, F. Alehan, Y. Y. Yalcin, G. Kubat, and F. B. Atac. 2015. Superoxide Dismutase and Catalase Genotypes in Pediatric Migraine Patients. *Journal of Child Neurology* 30:1586–90.

Scharff, L., D. C. Turk, and D. A. Marcus. 1995. Triggers of headache episodes and coping responses of headache diagnostic groups. *Headache* 35:397–403.

Schurks, M., R. Y. Zee, J. E. Buring, and T. Kurth. 2008. Interrelationships among the MTHFR 677C>T polymorphism, migraine, and cardiovascular disease. *Neurology* 71:505–13.

Sebastiao, A. M., and J. A. Ribeiro. 2000. Fine-tuning neuromodulation by adenosine. *Trends in Pharmacological Sciences* 21:341–46.

Seelig, M. S., B. M. Altura, and B. T. Altura. 2004. Benefits and risks of sex hormone replacement in postmenopausal women. *Journal of the American College of Nutrition* 23:482S–96S.

Shin, H. E., S. J. Han, K. S. Lee, and J. W. Park. 2011. Polymorphism of the Glutamate Transporter Protein EAAT2 and Migraine Transformation into Chronic Daily Headache. *Journal of Clinical Neurology* 7:143–47.

Shuen, A. Y., B. Y. Wong, C. Wei, Z. Liu, M. Li, and D. E. Cole. 2009. Genetic determinants of extracellular magnesium concentration: analysis of multiple candidate genes, and evidence for association with the estrogen receptor alpha (ESR1) locus. *Clinica Chimica Acta* 409:28–32.

Silaste, M. L., M. Rantala, M. Sampi, G. Alfthan, A. Aro, and Y. A. Kesaniemi. 2001. Polymorphisms of key enzymes in homocysteine metabolism affect diet responsiveness of plasma homocysteine in healthy women. *Journal of Nutrition* 131:2643–47.

Silberstein, S. D., and D. W. Dodick. 2013. Migraine genetics–a review: Part I. *Headache* 53:1207–17.

Sintas, C., O. Carreno, J. Fernandez-Morales, P. Cacheiro, M. J. Sobrido, B. Narberhaus, P. Pozo-Rosich, A. Macaya, and B. Cormand. 2012. A replication study of a GWAS finding in migraine does not identify association in a Spanish case-control sample. *Cephalalgia* 32:1076–80.

Society, H. C.CotI.H. 2004. The international classification of headache disorder. *Cephalalgia* 24(suppl 1):1–160.

Sparaco, M., M. Feleppa, R. B. Lipton, A. M. Rapoport, and M. E. Bigal. 2006. Mitochondrial dysfunction and migraine: evidence and hypotheses. *Cephalalgia* 26:361–72.

Stuart, S., H. C. Cox, R. A. Lea, and L. R. Griffiths. 2012. The role of the MTHFR gene in migraine. *Headache* 52:515–20.

Taylor, F. R. 2011. Nutraceuticals and headache: the biological basis. *Headache* 51:484–501.

Teigen, L., and C. J. Boes. 2015. An evidence-based review of oral magnesium supplementation in the preventive treatment of migraine. *Cephalalgia* 35:912–22.

Thomae, B. A., O. F. Rifki, M. A. Theobald, B. W. Eckloff, E. D. Wieben, and R. M. Weinshilboum. 2003. Human catecholamine sulfotransferase (SULT1A3) pharmacogenetics: functional genetic polymorphism. *Journal of Neurochemistry* 87:809–19.

Tuncel, D., F. I. Tolun, M. Gokce, S. Imrek, and H. Ekerbicer. 2008. Oxidative stress in migraine with and without aura. *Biological Trace Element Research* 126:92–97.

Uncini, A., R. Lodi, A. Di Muzio, G. Silvestri, S. Servidei, A. Lugaresi, S. Iotti, P. Zaniol, and B. Barbiroli. 1995. Abnormal brain and muscle energy metabolism shown by 31P-MRS in familial hemiplegic migraine. *Journal of the Neurological Sciences* 129:214–22.

Volinsky, R., and P. K. Kinnunen. 2013. Oxidized phosphatidylcholines in membrane-level cellular signaling: from biophysics to physiology and molecular pathology. *The Febs Journal* 280:2806–16.

Wang, Q., M. Ito, K. Adams, B. U. Li, T. Klopstock, A. Maslim, T. Higashimoto, J. Herzog, and R. G. Boles. 2004. Mitochondrial DNA control region sequence variation in migraine headache and cyclic vomiting syndrome. *American Journal of Medical Genetics. Part A* 131:50–58.

Wilson, C. W., J. G. Kirker, H. Warnes, and M. O'Malley. 1980. The clinical features of migraine as a manifestation of allergic disease. *Postgraduate Medical Journal* 56:617–21.

Woodbridge, P., C. Liang, R. L. Davis, H. Vandebona, and C. M. Sue. 2013. POLG mutations in Australian patients with mitochondrial disease. *Internal Medicine Journal* 43:150–56.

Yildirim, S., S. Akar, M. Kuyucu, A. Yildirim, S. Dane, and R. Aygul. 2011. Paraoxonase 1 gene polymorphisms, paraoxonase/arylesterase activities and oxidized low-density lipoprotein levels in patients with migraine. *Cell Biochemistry and Function* 29:549–54.

Zivadinov, R., K. Willheim, D. Sepic-Grahovac, A. Jurjevic, M. Bucuk, O. Brnabic-Razmilic, G. Relja, and M. Zorzon. 2003. Migraine and tension-type headache in Croatia: a population-based survey of precipitating factors. *Cephalalgia* 23:336–43.