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Genetic epidemiology of migraine and depression

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Abstract

Background: Migraine and major depressive disorder (commonly referred to as depression) are both common disorders with a significant impact on society. Studies in both clinical and community-based settings have demonstrated a strong relationship between migraine and depression. In addition to complicating the diagnosis, depression that is comorbid with migraine may lower treatment adherence, increase risk of medication overuse and is associated with migraine chronification, thus leading to higher direct and indirect costs and poorer health-related outcomes with increased disability.

Aim: The aim of this review is to summarise the current knowledge on the genetic epidemiology of migraine and depression and the possible biological mechanisms underlying their comorbidity.

Methods: We present a narrative review reporting on the current literature.

Results and conclusions: Epidemiological findings indicate that there is a bidirectional relationship between migraine and depression, with one disorder increasing the risk for the other and vice versa, suggesting shared biological mechanisms. Twin and family studies indicate that this bidirectional relationship can be explained, at least partly, by shared underlying genetically determined disease mechanisms. Although no genes have been robustly associated with the aetiology of both migraine and depression, genes from serotonergic, dopaminergic and GABAergic systems together with variants in the *MTHFR* and *BDNF* genes remain strong candidates.

Keywords

Migraine, depression, genetic, epidemiology, comorbid

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Introduction

Migraine is a common neurovascular disorder characterised by debilitating episodic headaches comprising two major subtypes: migraine with aura (MA) and migraine without aura (MO) (1). Approximately 23–30% (33–43% of all women and 13–18% of all men) will have recurring attacks of migraine during their life (2,3), with a female-to-male prevalence ratio ranging from 1.5:1 to 3.3:1 across the lifetime (2–6). From twin studies, it is known that migraine has on average 46% heritability (7), while from family and population association studies, the neural and vascular nature of such a genetic component was recently reviewed (8).

Major depressive disorder (MDD) is a psychiatric illness with lifetime prevalence estimates varying from 3% in Japan to 16.9% in the USA, with the majority in

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the range of 8–12% (9). Like migraine, MDD is twice as common among females than males (10,11). MDD patients are diagnosed based on the presence of associated symptoms such as loss of interest, depressed mood and suicidal ideation (12). The seriousness of such manifestations impact society at a level that ranked MDD as the second leading cause of disability worldwide in 2013 (13). Also similarly to migraine, the extent of the genetic component in MDD is estimated to be approximately 40–50% based on twin studies (14).

In spite of heterogeneous methodologies, epidemiological studies have been consistent in establishing an increased risk of depression in individuals with a history of migraine (15–20). For instance, some studies (15,17) reported that migraine sufferers were two- to three-times more susceptible to suffering from depression than their healthy counterparts, and the prevalence of MDD in migraineurs was significantly higher than in non-migraineurs, especially for migraineurs aged 18–38 years (16). Furthermore, other studies have shown that once the migraine–depression comorbidity is established, there is a bidirectional dose–response-type relationship; that is, the exacerbation of either one of these disorders is associated with a subsequent aggravation of symptoms in the other (18–20).

Longitudinal studies provide evidence of the temporal nature and direction of this relationship. Migraineurs have been shown to be 1.4–6-times more likely to experience a first onset of depression than non-migraineurs (15,21–24), and MDD patients are approximately 1.6–3.4-times more likely to develop migraine, particularly MA, than non-depressed individuals (18,24,25). These studies support a bidirectional association hypothesis in which the occurrence of one disorder would increase the risk of a first onset of the other, presuming the existence of shared genetic and environmental factors between migraine and depression (24,26). Alternatively, a causal theory, which assumes that the genetic and environmental factors of one disorder (e.g., migraine) account for the other (e.g., depression), has been proposed (25).

This review focuses on describing the current knowledge of the genetic aspects of comorbid migraine–depression and the possible biological mechanisms underlying this relationship. Identifying genetic overlap across phenotypes can help determine whether our current classification/categorisation of diseases is valid or whether genetic similarities traverse current divisions. This will be reflected in the development of more specific and effective treatments; for instance, the prescribed beta-blockers for migraine may exacerbate depression (27), or tricyclic antidepressants may prompt mania in bipolar patients (28). Additionally, when risk is correlated across phenotypes, pooled analyses will be better powered than individual-disorder analyses, thus improving the detection of genetic risk factors.

The first section of this review summarises the most relevant twin and family studies that support the shared genetic components between migraine and depression. The second section emphasises candidate gene studies whose results implicate common genetic variants in migraine and depression, whether in their comorbid or independent state, in relation to different cellular processes. The third section provides a current summary of the single-nucleotide polymorphisms (SNPs) identified by genome-wide association studies (GWAS) of migraine and depression and discusses the potential common SNP loci underlying these two conditions. Lastly, we discuss the main findings and provide recommendations for future studies of comorbid migraine and depression.

Twin and family studies

Twin and family studies provide natural experiments investigating the genetic and environmental vulnerability to complex traits such as migraine and depression, based on the principle that phenotype variance is affected by genetic factors, environmental factors and their interplay (29). Heritability is the proportion of phenotypic variation between individuals in a population that is attributable to individual genetic differences. The shared genetic components underlying two traits can be explained by the proportion of variation in a population due to shared genetics (i.e., bivariate heritability) and their genetic correlation (i.e., the genetic covariance normalised by the trait-specific heritabilities).

For instance, Schur et al. (30) performed bivariate structural equation modelling in a community-based sample of 758 monozygotic (MZ) and 306 dizygotic (DZ) female twin pairs, estimating a trait-specific heritability of 44% (95% confidence interval [CI]: 18–55%) for migraine and 52% (95% CI: 11–66%) for depression, and the authors estimated that 20% of the variance in migraine and depression is due to shared genetics (i.e., bivariate heritability of 20%). In other words, the genetic factors accounting for 44% of the variance in migraine also account for 20% of the variance in depression. A second study using 825 MZ and 666 DZ twins (31) estimated a heritability of 45% for migraine and 55% for anxious depression—a disorder that is highly correlated with MDD (32)—and determined that most (54%) of the covariance between migraine and anxious depression was explained by shared genetic factors. This study also estimated a genetic correlation between migraine and anxious depression of 0.30 (95% CI: 0.18–0.43). These findings indicate that the comorbidity of migraine and

depression can be explained, at least partly, by shared genetic factors.

More recently, Ligthart et al. (33) utilised genetic risk score (GRS) analysis and revealed a significant correlation in genetic risk across migraine and MDD. The GRS approach estimates genetic overlap across two traits by comparing trait values for one trait to a GRS for another trait. For example, a GRS for MDD was calculated in a 'target' sample of migraine cases and controls as a weighted count of MDD risk-associated SNP alleles identified in a 'discovery' MDD GWAS (34) for sets of SNPs with varying levels of significance (i.e., p-value <0.01, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9 and 1.0). Despite not differentiating between true- and false-positive SNP risk effects, such GRS analyses, using thousands of SNPs, are known to capture more genetic variance (compared to using a small number of highly significant SNPs) when there are more SNPs with smaller p-values than expected under the null hypothesis. That is, the excess in SNPs with smaller p-values reflects the true trait-associated polygenic signal, for which current GWAS simply do not have sufficient power to implicate at a genome-wide significant level. This novel study also provides evidence to suggest that, at least in a subset of individuals, migraine may be a result of MDD, and that migraine with and migraine without comorbid MDD may have different genetic aetiologies.

Although twin and family studies provide strong evidence for shared genetic components between migraine and depression, these studies are unable to identify the specific genetic (DNA sequence) variants. The identification of common specific genetic variants for migraine and depression has excellent potential to improve our understanding of the aetiology of migraine and comorbid depression and can be conducted by two main approaches: candidate gene association studies (CGAS) and GWAS.

Candidate gene association studies

CGAS can implicate genetic variants in a putative candidate gene by comparing their occurrence in individuals with the trait (cases) to their occurrence in individuals without the trait (controls) (35). Due to their relatively simple study design and low cost, CGAS have historically been the primary approach that has been used to investigate the role of genes in the pathogeneses of complex disorders such as migraine and depression. Candidate genes are selected based on their known and/or predicted biological function and potential to integrate with current theories of pathophysiology. In this paper, we performed a comprehensive review of CGAS for migraine (i.e., we searched PubMed using the terms "migraine" and "candidate gene study"). We then searched PubMed in order to identify overlapping CGAS for depression (using the terms "depression", one migraine candidate gene [e.g., "*SLC6A4*"] and "candidate gene study"). Table 1 presents a summary of the identified candidate gene studies that have been carried out in migraine and depression. The overlapping candidate genes suggest potential shared mechanisms underlying migraine and depression, possibly via serotonin and dopamine dysfunction, folate metabolism, the GABAergic system and growth factor activity.

Serotonin transporter *SLC6A4* and tryptophan hydroxylase 2 *TPH2*

Serotonin or 5-hydroxytryptamine (5-HT) dysfunction has been implicated in both migraine and depression pathogenesis. The serotonin transporter gene *SLC6A4* (or *5-HTT* or *SERT*; located on chromosome 17), particularly its 44-bp degenerate repeat polymorphic region (i.e., serotonin transporter-linked polymorphic region) 5-HTTLPR (with two common variations: a short variant [*s* allele] and a long variant [*l* allele]), is related to modulating neuronal expression of 5-HT transporter (36) and plays an important role in the serotonergic system. Migraine risk is possibly increased with lower levels of 5-HT, which can influence cortical spreading depression variance via excitability of the visual cortex (37), the central neurochemical imbalance via vasoconstriction (38) and the nociceptive trigeminal inhibition tension suppression system (39). Furthermore, some antidepressants that are related to the functional reduction of 5-HT levels can effectively remit some depressive symptoms such as sleep disturbance and depressed mood (40), and also reduce migraine attack frequency (41).

Previous studies have reported both positive and negative results regarding the association between 5-HTTLPR and migraine/depression susceptibility (42–47). In terms of migraine, for instance, Juhasz et al. (42) found a borderline nominal association between the 5-HTTLPR *s* allele and migraine (odds ratio [OR]: 1.45; 95% CI: 1.00–2.12; $p = 0.049$). However, the association was not significant ($p = 0.12$) when comparing 5-HTTLPR genotypes. A positive association was also identified from a recent meta-analysis (43) that showed that 5-HTTLPR was significantly associated with European female migraineurs carrying the *s* allele (OR: 2.02; 95% CI: 1.24–3.28). In terms of depression, a recent Korean study (44) detected that both the *s* allele and genotype frequencies of 5-HTTLPR were significantly associated with depression (adjusted p-value = 0.050 for allelic association; adjusted p-value = 0.015 for genotypic association). In a haplotype analysis (45), a significant

Table 1. Genes that have undergone association studies in both migraine and depression.

Pathogenesis	Gene	Migraine diagnosed according to the International Headache Society (IHS) criteria							Depression diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria						
		First author, year	Race/origin	Case/control	Variation	OR (95% CI)	*p*-value	Adjusted *p*-value[a]	First author, year	Race/origin	Case/control	Variation	OR (95% CI)	*p*-value	Adjusted *p*-value
Serotonin dysfunction	*SLC6A4*	Juhasz, 2003	Hungarian/Caucasian	126/101	5-HTTLPR	1.45 (1.00–2.12) – –	0.049 NS (AA) NS (GA)	– – –	Lopez-Leon, 2008[b]	Mixed	3752/5707	5-HTTLPR	1.11 (1.04–1.19)	<0.05	–
		Schurks, 2010[b]	Mixed	854/883	5-HTTLPR	2.02 (1.24–3.28)	<0.05	–	Haenisch, 2013	German	1505/2168	5-HTTLPR	1.14 (1.04–1.25)	<0.05	0.0154
		Wieser, 2010	German	58 MA/235 MO	5-HTTLPR	–	NS	–	Lee, 2014	Korean	186/1032	5-HTTLPR	– –	0.038 (AA) 0.015 (GA)	0.050 (AA) 0.015 (GA)
	TPH2	Marziniak, 2009	German/Caucasian	266/153	rs4570625 rs4341581 rs11178997 rs4565946	– – – –	NS NS NS NS	– – – –	Zill, 2004	German/Caucasian	300/265	rs1386494	0.60	0.0012	0.012
									Van Den Boaert, 2006	Swedish	135/364	rs11178997	–	<0.05	0.001
		Jung, 2010	German/Caucasian	503/515	rs1487275 rs1386486	0.47 (0.25–0.89) 0.56 (0.33–0.94)	0.02 0.03	NS NS	Wang, 2015	Chinese	190/155	rs7305115 rs4290270	– –	NS NS	– –
Dopamine dysfunction	*DAT1*	Karwautz, 2008	–	205 trios	40-bp VNTR	–	NS	-	Lopez-Leon, 2008	Mixed	151/272	40-bp VNTR	2.06 (1.25–3.40)	<0.05	–
		Todt, 2009	German/Caucasian	636/643	rs40184	0.81 (0.69–0.95)	0.0082	0.032	Haeffel, 2008	Russian	Total 176	rs40184	–	0.003	–
	DBH	Lea, 2000	Australian/Caucasian	177/182	rs72393728	–	<0.05	0.019	Zhou, 2015	Chinese	313/318	rs72393728	1.72 (1.20–2.47)	0.003	–
		Ghosh, 2011	Indian	301/302	rs72393728	1.50 (1.08–2.08) (AA) 2.02 (1.09–3.73) (GA)	<0.05 (AA) <0.05 (GA)	<0.016 (AA) <0.025 (GA)							
	DRD2	Peroutka, 1997	–	129/121	*NcoI*	–	<0.005	–	Peroutka, 1998	Mixed	Total 242	*NcoI*	–	<0.00002	–
		Peroutka, 1998	Mixed	Total 242	*NcoI*	–	<0.00002	–							
		Dichgans, 1998	–	47 MA/55 MO	*NcoI*	–	NS	–							
		Stochino, 2003	Sardinian/Italian	100 trios	*NcoI*	–	NS	–							
		Ghosh, 2011	Indian	301/202	*NcoI*	–	NS	–							
		Ghosh, 2013	Indian	335/200	*NcoI*	0.75 (0.61–0.93) (AA) 0.61 (0.43–0.89) (GA)	<0.05 (AA) <0.05 (GA)	0.04 (AA) 0.04 (GA)							
	DRD4	Zompo, 1998	Sardinian/Italian	Total 50 trios	48-bp VNTR	–	NS	–	Lopez-Leon, 2008[b]	Mixed	319/808	48-bp VNTR	1.73 (1.29–2.32)	≤0.001	–
		Mochi, 2003	Italian	194/117	48-bp VNTR	–	<0.05	0.0009							
Folate metabolism	*MTHFR*	Rubino, 2009[b]	Mixed	2710/3844	C677T	1.66 (1.06–2.59)	0.0002	–	Kelly, 2004	Ireland	100/89	C677T	1.90 (1.00–3.62)	0.03	–
		Schurks, 2010[b]	Mixed	6446/24578	C677T	1.48 (1.02–2.13)	<0.0001	–	Lopez-Leon, 2008[b]	Mixed	875/3859	C677T	1.20 (1.07–1.34)	<0.05	–
		Samaan, 2011	British/Caucasian	447/1402	C677T	1.31 (1.01–1.70)	0.039	–	Wu, 2013[b]	Mixed	4992/17082	C677T	1.76 (1.30–2.38) (Asian) 1.15 (1.01–1.31) (Caucasian)	<0.001 0.042	– –
		Liu, 2014[b]	Mixed	8903/27637	C677T	1.62 (1.13–2.32)	<0.05	–							
GABAergic system	*GABRQ*	Fernandez, 2008	Australian/Caucasian	275/275	rs3810651	–	NS	–	Pu, 2013	Chinese	Total 281	rs3810651	5.26 (1.68-16.49)	<0.05	0.001
		Quintas, 2013	Portuguese	188/286	rs3810651	4.07 (1.71–9.73)	0.002	<0.05							
	GABRA3	Quintas, 2013	Portuguese	188/286	rs3902802 rs2131190	0.41 (0.21–0.78) 0.53 (0.32–0.88)	0.006 0.013	<0.05 <0.05	Henkel, 2004	German/Caucasian	201/151	CAn	–	≤0.0001	–
Growth factor activity	*BDNF*	Lemos, 2010	Portuguese	188/287	rs2049046	1.88 (1.20–2.93)	<0.05	0.005	van Winkel, 2014	Belgian/Caucasian	Sample 1: 127 Sample 2: 446	rs2049046	– –	0.003 0.001	– –
		Sutherland, 2014	Australian/Caucasian	227/227	rs2049046	–	0.0125	–							

OR: odds ratio; CI: confidence interval; MA: migraine with aura; MO: migraine without aura; NS: not statistically significant at 5% level; AA: allelic association; GA: genotypic association; VNTR: variable number tandem repeat.

[a]The adjusted *p*-value—using methods such as Bonferroni correction and permutation—controls for the increased chance of false-positive findings due to multiple testing.

[b]Meta-analysis.

association was reported between the 5-HTTLPR TA haplotype (tagging *s* allele) and MDD (OR: 1.14; 95% CI: 1.04–1.25). Moreover, a large meta-analysis by Lopez-Leon et al. (46) reviewed 183 case–control genetic association studies of MDD and identified a significant OR of 1.11 (95% CI: 1.04–1.19) for the *SLC6A4* 5-HTTLPR *s* allele compared with the *l* allele. To date, the only study (47) that investigated 5-HTTLPR with respect to comorbid migraine and depression failed to identify an association between 5-HTTLPR and either migraine attack frequency or depression risk.

As a rate-limiting enzyme involved in 5-HT biosynthesis, tryptophan hydroxylase 2 (*TPH2*; located on chromosome 12) is possibly relevant to migraine and depression susceptibility via the reduction of 5-HT levels. Two studies have focused on investigating the association between *TPH2* and migraine risk (48,49). Jung et al. (48) revealed that two possible *TPH2* SNPs—rs1487275 (OR: 0.47; 95% CI: 0.25–0.89) and rs1386486 (OR: 0.56; 95% CI: 0.33–0.94)—were associated with migraine, but the results became non-significant after Bonferroni correction. However, a significant association between *TPH2* haplotype (TTGGG) and migraine was observed (adjusted p-value = 0.043), particularly for MO (adjusted p-value = 0.006), although another study failed to replicate this association (49). Some studies have reported *TPH2* polymorphisms being associated with depression onset (50,51). As an example, Zill et al. (50) performed the first analysis of *TPH2* in MDD. In this study, the *TPH2* SNP rs1386494 was found to be associated with MDD (adjusted p-value = 0.012), and three *TPH2* haplotypes (CGGCAATGAT, ATACGACGAT and CGGTAGTAGA) produced significant associations with MDD (adjusted p-values < 0.0001). Another study (51) identified one significantly associated *TPH2* haplotype (AGTT) tagging the SNP rs11178997 A allele (adjusted p-value = 0.001), and significant differences in this haplotype's distribution between cases and controls (adjusted p-value = 0.002). However, a more recent study (52) failed to identify associations between the *TPH2* SNPs rs7305115 and rs4290270 from Chinese MDD patients and controls.

These studies suggest that, at least in Caucasian populations, the *s* allele of *SLC6A4* 5-HTTLPR is possibly associated with an increased risk of both migraine and depression. However, we note that there were several negative results for the association between 5-HTTLPR and migraine and no positive report for Asians, implying that this association may be race specific. A similar pattern of results for *TPH2* suggests that *TPH2* SNPs may only contribute to the risk of migraine and depression in Caucasian populations.

Dopaminergic neurotransmission

A growing body of evidence suggests that a dysfunctional dopaminergic system may be the mechanism underlying the symptoms of yawning and somnolence ('sleepiness') in migraine (53) and the lack of motivation and attention in depression (54). This hypothesis is further supported by the use of dopamine agonists and antagonists as migraine (55) and depression (56) treatments in current medical practice, as well as by the coexistence of these two disorders with disorders such as Parkinson's disease (57), whose aetiology has been strongly associated with dopamine depletion (58).

Although inconsistent, genetic studies support a plausible role of the dopaminergic systems in migraine and depression. Particular interest has been given to polymorphisms in the dopamine D2 receptor (*DRD2*) gene, which is related to activation and sensitisation of the trigeminovascular complex (59). The *NcoI* C to T allelic variant located in exon 6 was evaluated in one study in which migraine subjects were also tested for depression and other mood disorders. In this study, individuals carrying the *NcoI* C allele had significantly more MA and MDD than the *NcoI* T allele carriers ($p < 0.00002$) (60). Similar results from 'migraine-only' populations were reported by the same authors in an independent MA cohort ($p < 0.005$) (61) and by Ghosh et al. in a total migraine sample (adjusted p-value = 0.04) (62). However, other studies (63–65) did not replicate the association of the *DRD2 NcoI* polymorphism with migraine.

Studies carried out independently in patients with migraine and depression have implicated a 48-bp variable number tandem repeat (VNTR) polymorphism located in exon 3 in the dopamine D4 receptor (*DRD4*) gene (66–68). A meta-analysis by Lopez Leon et al. reported a higher risk for MDD in two-repeat allele carriers (OR: 1.73; 95% CI: 1.29–2.32) (66), while Mochi et al. (67) found a significantly increased frequency of the four-repeat allele in a sample MO patients (adjusted p-value = 0.0009). However, another study did not find an association between the *DRD4* 48-bp VNTR and migraine (68).

While dopamine exerts its effects by binding and activating different subtypes of receptors, the termination of the stimulation signal on the synaptic and extra-synaptic membranes is caused by the interaction with dopamine transporters (DAT) (56). Polymorphisms in *DAT1* (also known as *SLC6A3*) have been investigated due to their possible influence on dopamine export rates from the synaptic cleft (56). Firstly, the A allele of the SNP rs40184, a variant located in exon 14 of *DAT1*, was associated with MA (OR: 0.81; 95% CI: 0.69–0.95) (69). Although no subsequent studies have tested for an association between

rs40184 and MA, one study reported a higher risk of depression ($p = 0.003$) in Russian male adolescents who have experienced maternal rejection and are carrying the AA genotype (70). Noticeably, in this study, the A allele was more abundant in cases, thus opposing the protective effect detected in migraine patients. Association studies testing a VNTR polymorphism located in the 3́-untranslated region of *SLC6A3* have produced negative results for migraine (71) and inconsistent results for depression (46).

The dopamine beta-hydroxylase (*DBH*) gene encodes an enzyme that is involved in maintaining the balance of dopaminergic neurotransmission by catalysing the conversion of dopamine to norepinephrine (72). An Australian study (73) described a significantly different (adjusted p-value = 0.019) allele distribution of the *DBH* dinucleotide (AC) repeat in migraineurs. This polymorphism is in high linkage disequilibrium with a 19-bp insertion/deletion (rs72393728) in the same gene, whose D (deletion) allele was reported to be associated with female migraineurs (OR: 1.50; 95% CI: 1.08–2.08) (65). Remarkably, the same allele seems to increase susceptibility to MDD in a Chinese Han population (OR: 1.72; 95% CI: 1.20–2.47) (74).

In the light of previous reports, the dopaminergic system may play a complex role in both migraine and depression susceptibilities via multiple polymorphisms, including the 48-bp VNTR in *DRD4*, rs40184 in *DAT1* and rs72393728 in *DBH*. However, it is still ambiguous whether these variants act independently or interact in order to increase risk of migraine and depression. Thus, attention should focus on larger studies in order to replicate these results and better define the role of these variations in the aetiology of migraine and depression.

MTHFR

The *MTHFR* gene encodes the methylenetetrahydrofolate reductase enzyme (MTHFR), which catalyses the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, the most abundant circulating form of folate. In turn, folate is a co-substrate of the synthesis of methionine from homocysteine; MTHFR dysfunction has been associated with pain in migraine via hyperhomocysteinaemia (75) and with different central nervous systems disorders, including depression, by limiting the synthesis and presynaptic release of dopamine as a consequence of low folate levels (76).

Numerous studies have tested for associations between the C677T polymorphism (rs1801133) and migraine and depression susceptibility (46,77–82). This SNP causes the synthesis of a thermolabile MTHFR variant that is characterised by reduced activity. A meta-analysis by Rubino et al. showed that the T allele provided susceptibility to MA (OR: 1.66; 95% CI: 1.06–2.59) (77). These results were later replicated by another meta-analysis reporting increased susceptibility for MA in TT genotype carriers (OR: 1.48; 95% CI: 1.02–2.13). Interestingly, this association was not found when only populations of Caucasian ancestry were analysed, prompting the conclusion of an association that has been driven by the one Asian cohort included in the study (OR: 6.54; 95% CI: 2.54–16.81) (78). This observation was further confirmed by the most recent and largest meta-analysis of 17 studies (79). In this study, Liu et al. identified a significant association between the T allele and migraine risk exclusively in the Asian population (OR: 1.62; 95% CI: 1.13–2.32), with this being particularly strong in the MA subgroup (OR: 2.00; 95% CI: 1.01–3.95). Remarkably, a number of *MTHFR* gene association results in depressed individuals greatly resemble those obtained in migraineurs (46,80,81). For instance, in the most recent meta-analysis, Wu et al. (81) reported that Asian individuals carrying the 677T allele had an increased risk of suffering from depression (OR: 1.76; 95% CI: 1.30–2.38) compared to Caucasians (OR: 1.15; 95% CI: 1.01–1.31). Although no studies have specifically investigated the C677T variant in a comorbid migraine and depression sample, Samaan et al. (82) compared 447 individuals with migraine to 1402 individuals without migraine who were recruited from a genetic case–control association study of recurrent major depression. In this study, the *MTHFR* C677T polymorphism was associated with MA, and this association remained significant after adjusting for age, sex and depression status (OR: 1.31, 95% CI: 1.01–1.70).

In summary, the C677T polymorphism in *MTHFR* has been reported to be associated with both migraine and depression risk, with stronger effects observed in Asian compared to Caucasian populations. The association is strongest with migraine and especially MA, and it has been suggested that low folate levels may induce aura symptoms (83).

GABA receptor *GABRQ* and *GABRA3*

The activation of gamma-aminobutyric acid (GABA)-A receptor by GABA inhibits neurotransmission signalling by means of Cl^- channel permeabilisation and the subsequent establishment of an inhibitory postsynaptic potential (84). Thus, the GABAergic system not only regulates the excitability of nociceptive neurons and the pain threshold in the trigeminal nucleus caudalis, which is related to migraine pathogenesis, but also exerts its inhibitory action on the hypothalamic–pituitary–adrenal axis, which is involved in depression (85). Furthermore, the GABAergic system seems to play a role in modulating ovarian hormone fluctuations (e.g., oestrogen and progesterone) (86), which may

explain why both migraine and depression are more prevalent in females than in males.

Two chromosomal regions in particular— 15q11–13 and Xq24–28, containing genes encoding the GABA-A receptor subunits—have been the focus of association studies since earlier linkage analyses suggested a possible relationship with migraine (87,88). For example, Quintas et al. demonstrated an association with migraine for the SNP rs3810651 in *GABRQ* (OR: 4.07; 95% CI: 1.71–9.73), and for the SNPs rs3902802 (OR: 0.41; 95% CI: 0.21–0.78) and rs2131190 (OR: 0.53; 95% CI: 0.32–0.88) in *GABRA3*. The *GABRQ* and *GABRA3* genes are both located on chromosome Xq24–28 and encode the γ- and α3-GABA-A subunits, respectively (89). However, another study in an Australian sample did not replicate these findings (90). Strikingly, the SNP rs3810651—a missense variation in exon 9 of *GABRQ*—has been separately associated (OR: 5.26; 95% CI: 1.68–16.49) with MDD patients who were given antidepressants for 6 weeks (91). Additionally, Henkel et al. reported a significantly different allelic distribution ($p \leq 0.0001$) of the dinucleotide (CA) repeat polymorphism located in intron 8 of *GABRA3* among female unipolar depression patients (92).

Although only a small number of studies have focused on investigating the GABAergic system with respect to migraine and depression risk, it is nonetheless worth noting that different genetic variants in *GABRA3* and the same variant (rs3810651) in *GABRQ* have been associated with an increased risk of migraine and depression.

Brain-derived neurotrophic factor *BDNF*

By means of dopaminergic and serotonergic neuron modulation, *BDNF* controls the regions implicated in pain, mood and behaviour in the central nervous system (93). Here lies the implication of this gene in migraine and depression pathogenesis. Although no previous studies have evaluated the relationship between genetic variants and comorbid migraine–depression, a number of independently performed association studies suggest a possible effect on the two phenotypes.

The *BDNF* rs2049046 T allele has been associated with MA ($p = 0.0125$) in an Australian sample (94), and although no individual SNP analyses have replicated this result, one study reported a higher risk of migraine (OR: 1.88; 95% CI: 1.20–2.93) in double heterozygotes rs2049046-AT and rs1553005-GC, with the latter being a SNP that is located in the calcitonin gene-related peptide (*CGRP*) gene (95). The rs2049046 SNP has also been associated with antidepressant efficacy in depressed patients (96). The Val66Met (rs6265) SNP is another well-studied polymorphism in the *BDNF* gene. It has been suggested that Met allele carriers secrete less *BDNF* protein than their counterparts, and that, among others outcomes, they might have an increased risk of suffering from depression (97). However, there is a lack of positive findings on this matter, and so far, no plausible role has been attributed to the Val66Met polymorphism (94) in migraine. Rather, the *BDNF* SNP rs2049046 seems to be associated with both migraine and depression susceptibility. One migraine-related study suggested an interaction between rs2049046 and rs1553005 (95); however, this finding awaits replication.

Genome-wide association studies

GWAS have proven to be a powerful approach for detecting common variants associated with complex diseases (98). To date, six GWAS have been completed in migraine and are reviewed in detail elsewhere in this issue (99). Anttila et al. (100) reported the first migraine GWAS SNP locus—rs1835740—near *MTDH* and *PGCP* on 8q22.1 ($p = 5.38 \times 10^{-9}$) using a large case–control sample of individuals with European ancestry (2731 MA cases and 10,747 controls). The largest published study, utilising 23,285 migraine cases and 95,425 population-matched controls, reported five novel SNP loci (near *AJAP1*, near *TSPAN2*, in *FHL5*, in *C7orf10* and near *MMP16*) and confirmed seven previously implicated SNP loci (in *PRDM16*, in *MEF2D*, in *TRPM8*, near *TGFBR2*, in *PHACTR1*, in *ASTN2* and in *LRP1*) to be significantly associated with migraine ($p < 5 \times 10^{-8}$) (101).

Despite MDD having a similar heritability to migraine, until the present year, attempts to robustly identify genetic risk variants for MDD have been unsuccessful (102). Thus, in what is considered by some as the ''beginning of the beginning for the genetic dissection of MDD'' (103), the China Oxford and VCU Experimental Research on Genetic Epidemiology (CONVERGE) consortium published a GWAS that was wisely designed to overcome the limitations faced by previous attempts (104). Selecting 5303 Han Chinese women with recurrent and severe MDD and 5337 healthy female controls, the authors reported significant associations ($p < 5 \times 10^{-8}$) with the SNPs rs12415800 (in *SIRT1*) and rs35936514 (in *LHPP*), which are implicated in mitochondria functioning and transcription signalling, respectively. Importantly, both rs12415800 ($p = 7.71 \times 10^{-4}$) and rs35936514 ($p = 1.68 \times 10^{-4}$) were convincingly replicated in a separate Han Chinese cohort of 3231 cases with recurrent MDD and 3186 controls. Although this is the first time that a mitochondrial gene has been implicated in depression, the dysfunction of this organelle as a key factor in the onset of depression was previously hypothesised by the same authors and others (105).

Interestingly, migraine has also been linked to mitochondrial dysfunction, and recent studies have implicated mtDNA variants (106), albeit located in different genes.

Recently, the SNP rs1160720 (near *NBEA* on 13q13.3) was found to be significantly associated with comorbid bipolar disorder and migraine ($p = 2.97 \times 10^{-8}$) by comparing 460 bipolar migraineurs and 914 bipolar patients without migraine (107). Although bipolar disorder shares signs and symptoms with depression, association of this SNP was not observed ($p > 0.05$) in the 2013 Psychiatric Genomics Consortium (PGC) MDD GWAS (102) (https://www.med.unc.edu/pgc/files/resultfiles/pgc.mdd.2012-04.zip) and the 2013 International Headache Genetics Consortium (IHGC) migraine GWAS (101).

The GWAS-implicated genetic risk loci for migraine and MDD are both novel and recent; hence, candidate gene studies are yet to be performed in order to determine whether they contribute to both migraine and depression individually and/or comorbid migraine and depression. However, our interrogation of the published and publicly available MDD GWAS summary results indicates that the most significant SNP that is associated with migraine in the 2013 IHGC migraine GWAS (rs11172113 within *LRP1* on 12q13; $p = 3.94 \times 10^{-19}$) is also associated with MDD ($p = 1.35 \times 10^{-3}$) in the recent (2015) Han Chinese MDD GWAS (104) (https://www.med.unc.edu/pgc/files/resultfiles/converge.MDD.summary_stats.2Sep2015.tbl.gz), with the same allele (T) associated with increased risk for both migraine and depression (see Table 2 and Table 3). The *LRP1* gene is expressed in many tissues, including the brain, and is known to modulate synaptic transmission.

Concluding remarks

Twin and family studies have provided strong evidence for a common genetic component underlying migraine and depression comorbidity, suggesting that migraine with and migraine without comorbid MDD may have different genetic aetiologies. Indeed, recent results from full-brain magnetic resonance imaging studies finding comorbid migraine and MDD to be associated with smaller brain tissue volumes compared to having one or neither of these conditions (108) provide further support to the notion that migraineurs with MDD may represent a distinct clinical phenotype.

Despite the strong evidence for shared genetic components between migraine and depression, no specific genetic variant has been shown to have an unequivocal association with risk of both migraine and depression. Among the candidate gene variants that have been tested, the *s* allele of the 5-HTTLPR polymorphism located in *SLC6A4* and *MTHFR* C677T have provided the most consistent evidence of associations with both migraine and depression. The 48-bp VNTR in *DRD4*, rs72393728 in *DBH*, rs40184 in *DAT1*, rs3810651 in *GABRQ* and rs2049046 in *BDNF* also deserve

Table 2. Association results for genome-wide significant migraine risk loci.

						2013 IHGC migraine (all migraine samples)		2013 PGC MDD		2015 CONVERGE MDD	
IHGC migraine reported genes	Strongest SNP	Chromosome	A1	A2	MAF	OR	*p*-value	OR	*p*-value	OR	*p*-value
PRDM16	rs2651899	1	C	T	0.41	1.09	4.35×10^{-14}	0.98	0.3119	1.00	0.8129
Near *AJAP1*	rs10915437	1	G	A	0.36	0.95	6.13×10^{-4}	0.98	0.4632	0.99	0.1412
Near *TSPAN2*	rs12134493	1	A	C	0.12	1.14	4.79×10^{-14}	1.01	0.8637	0.99	0.6685
MEF2D	rs2274316	1	C	A	0.36	1.07	1.42×10^{-8}	0.99	0.7326	1.00	0.9083
TRPM8	rs6741751	2	A	G	0.10	0.87	3.34×10^{-13}	0.99[a1]	0.7003	0.99	0.5498
Near *TGFBR2*[b]	rs6790925	3	T	G	0.38	1.05	8.74×10^{-5}	1.00	0.9935	0.99	0.0706
PHACTR1	rs9349379	6	G	A	0.41	0.93	4.60×10^{-8}	1.04	0.0796	1.00[a3]	0.6868
FHL5	rs13208321	6	A	G	0.22	1.10	1.35×10^{-11}	1.02	0.5082	0.99	0.2644
c7orf10	rs4379368	7	T	C	0.11	1.11	1.07×10^{-9}	1.07	0.0495	0.99	0.0867
Near *MMP16*	rs10504861	8	T	C	0.16	0.96	3.53×10^{-3}	1.03[a2]	0.2692	1.00	0.6709
ASTN2	rs6478241	9	A	G	0.38	1.06	4.43×10^{-7}	1.00	0.9630	1.00	0.7014
LRP1	rs11172113	12	C	T	0.43	0.90	3.94×10^{-19}	1.00	0.8769	0.97	0.0013

OR and *p*-value are associated with minor allele (A1).

A1: minor allele; A2: other allele; SNP: single-nucleotide polymorphism; MAF: minor allele frequency; MDD: major depressive disorder; OR: odds ratio.

[a]The strongest SNP is not available in the MDD association studies. Alternatively, we select their correlated SNP (highest linkage disequilibrium (LD) and closest distance): [a1] rs7577262 (LD $r^2 = 1$); [a2] rs6990990 (LD $r^2 = 0.943$); [a3] rs13211739 (LD $r^2 = 0.347$).

[b]One candidate gene study reported a non-significant ($p = 0.452$) association between *TGFBR2* and medication-free MDD patients (25 cases; 25 controls).

Table 3. Association results for genome-wide significant major depressive disorder risk loci.

						CONVERGE MDD		2013 IHGC migraine (all migraine samples)	
CONVERGE MDD reported genes	Strongest SNP	Chromosome	A1	A2	MAF	OR	*p*-value	OR	*p*-value
SIRT1	rs12415800	10	A	G	0.45	1.15	2.53×10^{-10}	–	–
LHPP	rs35936514	10	T	C	0.26	0.84	6.45×10^{-12}	1.02[a]	0.2597

OR and *p*-value are associated with minor allele (A1).

MDD: major depressive disorder; A1: minor allele; A2: other allele; SNP: single-nucleotide polymorphism; MAF: minor allele frequency; OR: odds ratio; –: The correlated SNP has LD $r^2 < 0.1$.

[a]The strongest SNP is not available in the migraine association results. Alternatively, we select their correlated SNP (highest linkage disequilibrium (LD) and closest distance): rs12264955 (LD $r^2 = 0.425$).

consideration for future study in larger, more powerful samples. Similarly, our observation that rs11172113 in *LRP1* is associated with risk of migraine ($p = 3.94 \times 10^{-19}$) and MDD ($p = 1.35 \times 10^{-3}$) in large independent GWAS warrants further investigation. In addition, the different results observed for Caucasian and Asian CGAS samples may be complicated by the lower prevalence observed in Japan for both migraine (109) and depression (9); hence, larger studies in both Caucasian and Asian populations are required.

It is important to reiterate that none of these candidate genes and their risk loci were associated with both migraine and MDD by GWAS data at either genome-wide significant ($p < 5 \times 10^{-8}$) or suggestive ($p < 1 \times 10^{-5}$) level. A similar conclusion was drawn from the study by de Vries et al. (110), which reported no experiment-wide significant results for the selected candidate genes that had previously been associated with migraine. The most likely reason for GWAS not supporting previously implicated candidate genes relates to the typically small sample sizes used in CGAS, which increase the chance of generating both false-positive and false-negative results (111). Other explanations include the possibility that candidate gene findings may be specific to a particular sample, which, due to differences in ascertainment, may not be observed in large heterogeneous GWAS case samples. However, published methods for the CGAS indicate similar ascertainment approaches and diagnoses to those used in GWAS. Additionally, CGAS often focus on a limited number of variants in a target gene that may not be well represented ('tagged') in the GWAS genotyping arrays. As a consequence, candidate gene variants, especially those with minor allele frequencies lower than 0.05–0.10, may be less likely to be identified by GWAS that utilise common ('tag') SNPs. Finally, publication bias is another potential source of false-positive findings in CGAS, mainly caused by the fact that studies with positive results are more likely to be published than those with negative results. The specificity in the diagnosis will also likely play a key role in future CGAS and GWAS designs. The utility of such is demonstrated by the use of female-only severe recurrent depression cases in the only successful MDD GWAS (104).

Given the strong evidence of shared genetic risk across migraine and depression, association analysis in migraine should benefit from careful screening/diagnosis of migraine cases and controls for depression, and vice versa, in order to allow for subgroup and adjusted analyses. Indeed, as illustrated by studies of the C677T variant in *MTHFR*, once the comorbidity adjustments were performed, the association remained only in the MA population, suggesting that previous associations of this gene with depression may have been confounded by the presence of MA in the depressed cohort.

SNPs in candidate gene studies should also possess a good rationale for their selection. This will minimise negative outcomes and allow for the further confirmation of previously associated variants from GWAS or other candidate genes studies. Finally, we encourage the implementation of new technologies such as whole-genome sequencing in order to assess comprehensively genetic variation across (implicated) regions and so identify the likely causal genetic risk factors.

We believe that improved study design utilising appropriate sample sizes, detailed phenotyping of both cases and controls, stratification by migraine type and depression status/symptoms and adjustment for comorbid and genetically correlated traits will be key to determining the specific genetic factors that underlie the 20% of variance in migraine and depression due to shared genetics.

Article highlights

- Migraine and depression are comorbid disorders that pose significant burdens on society. At least 20% of the variance in migraine and depression is due to shared genetics.
- Genes from the serotonergic, dopaminergic and GABAergic systems together with variants in the *MTHFR* and *BDNF* genes have been implicated in the aetiology of migraine and depression.
- Currently, no genes have been robustly associated with the aetiology of both migraine and depression. Future studies should make use of large, well-characterised samples of migraine cases with comorbid depression.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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