RESEARCH ARTICLE

The association between migraine and depression based on miRNA biomarkers and cohort studies

Yi-Hau Chen[1] and Hsiuying Wang[2,*]

[1]*Institute of Statistical Science, Academia Sinica, Nankang, Taipei, Taiwan;* [2]*Institute of Statistics, National Chiao Tung University, Hsinchu, Taiwan*

Abstract: ***Background***: An association between migraine and Major Depression (MD) has been revealed in a number of clinical studies. Both diseases have affected a large global population. More understanding of the comorbidity mechanism of these two diseases can shed light on developing new therapies for their treatment.

Methods: To the best of our knowledge, there have not been any researches in the literature based on microRNA (miRNA) biomarkers to investigate the relationship between MD and migraine. In this study, we have discussed the association between these two diseases based on their miRNA biomarkers. In addition to miRNA biomarkers, we have also demonstrated epidemiological evidence for their association based on Taiwan Biobank (TWB) data.

Results: Among the 12 migraine miRNA biomarkers, 11 are related to MD. Only miR-181a has no direct evidence to be involved in the mechanism of MD. In addition to the biological biomarker evidence, the statistical analysis using the large-scale epidemiologic data collected from TWB provides strong evidence on the relationship between MD and migraine.

Conclusion: The evidence based on both molecular and epidemiological data reveals the significant association between MD and migraine. This result can help investigate the correlated underlying mechanism of these two diseases.

1. INTRODUCTION

Migraine is a prevalent neurovascular disease that has affected approximately 15% of people in the world [1]. It occurs more frequently in females than in males. Associated symptoms include throbbing and pulsating pain, light sensitivity, sound sensitivity, nausea, pain on one side, vision changes, blurred vision, aura, and vomiting. Migraine attacks usually last from 4 to 72 hours and a migraine taking longer than 72 hours is called Status Migrainosus (SM). SM is a rare disabling complication that might not respond to treatment [2]. The underlying mechanisms of the migraine are unknown. As the migraine symptoms have multiple phases, it is observed that multiple neuronal systems do not function normally [3]. Migraine might also start in childhood such that it might be considered a genetic disorder [4].

Migraine is a common comorbidity of autoimmune diseases [5]. There is a high prevalence of migraine in patients with systemic lupus erythematosus (SLE) [6]. Migraine is more prevalent in SLE patients and is associated with depression-like symptoms in the general population but not associated with disease activity or abnormalities [7]. Headache and migraine are common features in multiple sclerosis (MS) and can influence the quality of life of these patients [8]. Ophthalmoplegic migraine is associated with acute anterior uveitis [9], which is an autoimmune disease.

Several studies have revealed that migraine and Major Depression (MD) are often comorbid. MD is a serious mood disorder that affects the quality of daily life and health of people. The lifetime prevalence rate of MD was found to be higher in high income than in

* Address correspondence to this author at the Institute of Statistics, National Chiao Tung University, Hsinchu, Taiwan;
Fax: 886-3-5728745; Tel: 886-3-5712121;
E-mail: wang@stat.nctu.edu.tw

low-middle income countries [10]. MD is associated with several other diseases such as obesity, diabetes, cancer, stroke, and acute coronary syndrome [11-14]. To have a better understanding of this comorbidity, its epidemiology, pathophysiology, genetic and environmental factors, treatment, and prognosis, have all been explored [15]. The risk of MD was found to be increased in migraine patients aged over 65 years compared with healthy controls [16]. Logistic regression was applied to analyze the anxiety and depression aspects that were related to migraine using self-administered questionnaires completed by 782 patients. It revealed that physical depression symptoms were more linked to migraine than emotional symptoms [17]. Migraineurs are more likely to suffer from depression compared with non-migraineurs and the incidence of depression in migraineurs is highly variable [18].

The association between migraine and MD may also be explained using the pharmaceutical aspects that some drugs are effective in both diseases [19]. Venlafaxine () and amitriptyline () are two types of antidepressants often used to treat depression. Randomized trials of venlafaxine have provided preliminary evidence that this agent is effective in reducing headache frequency for migraine [19]. In patients with migraine with or without aura, the prophylactic effect of amitriptyline and venlafaxine was compared in a randomized, double-blind crossover study. Both drugs had a significant beneficial effect on pain parameters, but venlafaxine was suggested for the prophylaxis of migraine because of its low and/or tolerable side effect properties [20]. Venlafaxine was more effective and well-tolerated than placebo for migraine prophylaxis [21]. These studies revealed that MD and migraine might have some common pathologies, therefore, in this study, we investigate their relationship from the molecular viewpoint.

Although some related studies have discussed the relationship between MD and migraine, to the best of our knowledge, there have not been any previous researches investigating the use of microRNA (miRNA) biomarkers. In this study, we have explored the association between migraine and MD based on their miRNA biomarkers. First, we searched miRNA biomarkers of migraine in the literature and then checked whether these migraine miRNA biomarkers are related to MD. In addition to the study of their miRNA biomarkers, empirical data analysis from cohort studies of Taiwan Biobank (TWB) [22] was used to further validate our results. This data analysis shows the strong relationship between migraine and MD among Taiwanese people.

miRNAs have the potential to be involved in the treatment of various human diseases. For example, in the treatment of cancer, chemotherapy is majorly used. However, chemotherapy resistance can reduce the effect of the treatment. miRNA therapy is new hope for patients with therapeutic or drug resistance issues. Therapeutic miRNA, combined with chemotherapeutic agents, can reduce the drug doses for cancer treatment. As a result, miRNA-based therapeutics might be the next generation drugs for the cure of various diseases, and miRNA-based therapeutics will be available in the form of several new drugs in the market in the next two decades [23]. Therefore, the discussion of the common miRNA biomarkers in this study may help develop common miRNA therapeutics for both MD and migraine.

2. METHODS AND MATERIALS

2.1. microRNA

miRNAs are single-stranded and non-coding RNAs of about 22–24 nucleotides that were first discovered in the early 1990s while studying development in the nematode Caenorhabditis elegans [24, 25]. miRNAs contribute to the regulation of gene expression, cell proliferation, differentiation, apoptosis, and physiological processes [26]. miRNA are involved in mRNA degradation by binding to 3'-untranslated regions. It has been estimated that miRNAs may regulate up to 30% of the genes in the human genome [27, 28].

The role of miRNAs in migraine, including potential biomarkers, pathogenesis, and miRNA-based therapeutic options, has been discussed [29]. Besides, the use of miRNA biomarkers has been discovered for many other diseases. miRNA acts as a tumor suppressor by targeting specific genes [30]. High-confident miRNA biomarkers are predicted for various cancers [31-34]. In addition, miRNA may also contribute to neurological diseases and inflammation in the brain [35], such as amyotrophic lateral sclerosis, Parkinson's disease, and anti-NMDA receptor encephalitis [36, 37]. miRNA also contributes to the association between MD and gastroesophageal reflux disease (GERD) [38]. In addition, miRNA can be used to investigate the association between vaccines and anti-NMDA receptor encephalitis [39, 40]

2.2. microRNA Biomarkers of Migraine

A literature search was conducted to find miRNAs biomarkers of migraine. Then we searched the literature to link these migraine miRNA biomarkers to MD. These miRNA biomarkers, their references, and other information are listed in (Table **1**).

Table 1. miRNA biomarkers of migraine.

miRNA	Migraine reference	Description of Migraine	MD reference	Description of MD
miR-590-5p	[41]	It is modulated by celecoxib in mice and humans.	[42]	↓
miR-34a-5p	[43-45]	↑	[42]	↑
miR-382-5p	[43, 45]	↑	[46]	↑
miR-30a	[47]	↓	[48]	after treatment, ↑
miR-375	[44]	↑	[42]	↑
miR-27a	[45, 49]	↑	[50]	↑
miR-181a	[49]	↓	-	
let-7b	[49]	↓	[51]	↓
miR-22	[49]	↓	[52]	↓
miR-155	[53]	↑	[53]	↑
miR-126	[53]	↑	[54]	↑
Let-7g	[53]	↑	[55]	after treatment, ↑

"↑" denotes that the miRNA is upregulated; "↓" denotes the miRNA is downregulated.

We found 12 miRNA biomarkers (Table **1**) of migraine in the literature. miR-590-5p was found altered during a human migraine attack, as well as in mouse models with different pain conditions [41]. Migraine attacks were associated with an acute up-regulation of miR-382-5p and miR-34a-5p expression [43]. Higher expression of miR-34a-5p and miR-375 was discovered in the saliva of untreated young subjects with migraine without aura compared to healthy subjects [44]. Expression levels of miR-30a were significantly decreased in migraine patients and could relieve migraine through the degradation of the calcitonin/alpha-CGRP gene [47]. A circulating miRNAs profile in comparing migraineurs versus controls showed that miR-181a, let-7b, and miR-22 were significantly downregulated, while miR-27b was significantly upregulated [49]. Compared to control subjects, migraine patients had upregulated expression of miR-155, miR-126, and let-7g [53].

2.3. Taiwan Biobank Data

As an empirical validation of the relationship between MD and migraine, we consider the statistical association analysis based on data from the TWB. Specifically, the data are from the TWB community-based cohort, which consisted of more than 120,000 participants. The TWB data contain demography and health/symptom/disease information for study subjects, which are collected through questionnaires and are carefully examined/checked. For more details about TWB, please refer to the webpage [56]. Our analysis for the association between MD and migraine is based on the released subsample of the TWB community-based cohort consisting of 5000 randomly sampled subjects. The mean age of the subjects in the subsample is 48.8 years with a standard deviation of 10.8 years, and the male to female ratio in the subsample is 2445:2555.

3. RESULTS

3.1. miRNA Analysis

Among the 12 migraine miRNA biomarkers in (Table **1**), 11 of them are related to MD. Only miR-181a does not have direct evidence showing involvement in the mechanism of MD. The other 11 miRNAs have been discussed in related studies. The mean relative expression level in cerebrospinal fluid (CSF) of miR-590–5p in depressed patients was lower than in control patients. However, the expression levels of miR-34a and miR-375 in CSF were significantly higher than control subjects [42]. A significantly increased expression level in miR-382-5p was identified in the mouse chronic mild stress model of depression compared with the control group [46]. The mean plasma miR-30a-5p level in the depression/anxiety patients increased significantly compared to baseline [57]. miR-27a expression level in both hippocampal tissues and blood from rats with depression was upregulated [50]. The baseline expression of let-7b was less by ~40% compared with controls in treatment-resistant depression patients [51]. miR-22 was down-regulated in MD with upregulated target mRNA RUFY2 and down-regulated target mRNAs, FMNL2, PTGFR, CBL, OGN [52]. By the quantitative real-time poly-

merase chain reaction (PCR) analysis, the cellular and serum levels of miR-155 were upregulated in individuals with depression compared with those in healthy controls [53]. Patients with psychotic depression had elevated baseline levels of miR-126-3p compared to healthy controls [54]. The quantitative expression analysis indicated that the expression level of let-7g in the blood of MD patients was modulated by antidepressant treatment [55].

3.2. Taiwan Biobank Data Analysis

The TWB data analysis was used as an empirical validation for the relationship between MD and migraine. This analysis was based on a recent large cohort study, which is seen less frequently in the literature. The prevalence of MD in the TWB analysis subsample was found to be 2.98%, while that of migraine was 2.48% (Table **2**). The prevalence of MD in the TWB sample was slightly higher than the prevalence of 1.5% reported in Taiwan [58], while the migraine prevalence was relatively lower than the prevalence of 9.1% reported in a Taiwan population-based survey

[59]. On the other hand, consistent with the literature, the MD and migraine prevalence rates were found to be higher in females than in males. There were a total of 77 female and 47 male migraine cases, and 90 female and 59 male MD cases in this subsample. The prevalence rates of MD in female and male subjects of our TWB subsample were 3.52% and 2.41%, respectively; the prevalence rates of migraine in female and male subjects of our TWB subsample were 3.01% and 1.92%, respectively.

Based on the cross table, (Table **2**) from the TWB sample data, the odds ratio (OR) measuring the association between MD and migraine was obtained as 4.08 (95% confidence interval (CI): 2.24—7.43, p-value$<10^{-5}$). The results show a strong association between MD and migraine. The further analysis stratified by gender shows that the association between MD and migraine is stronger in females than in males: in females, the OR is 4.47 (95% CI: 2.22—9.02, p-value$<10^{-4}$), while in males, the OR is 2.85 (95% CI: 0.86—9.46, p-value: 0.19).

Table 2. Cross table of numbers of MD and migraine patients in the TWB sample. (a) overall sample; (b) female sample; (c) male sample.

(a) Overall

	MD			
Migraine	No	Yes	Row Total	Row %
No	4740	136	4876	97.52%
Yes	111	13	124	2.48%
Column Total	4851	149		
Column %	97.02%	2.98%		

(B) Female

	MD			
Migraine	No	Yes	Row Total	Row %
No	2398	80	2478	96.99%
Yes	67	10	77	3.01%
Column Total	2465	90		
Column %	96.48%	3.52%		

(C) Male

	MD		Row Total	
Migraine	No	Yes		Row %
No	2342	56	2398	98.08%
Yes	44	3	47	1.92%
Column Total	2386	59		
Column %	97.59%	2.41%		

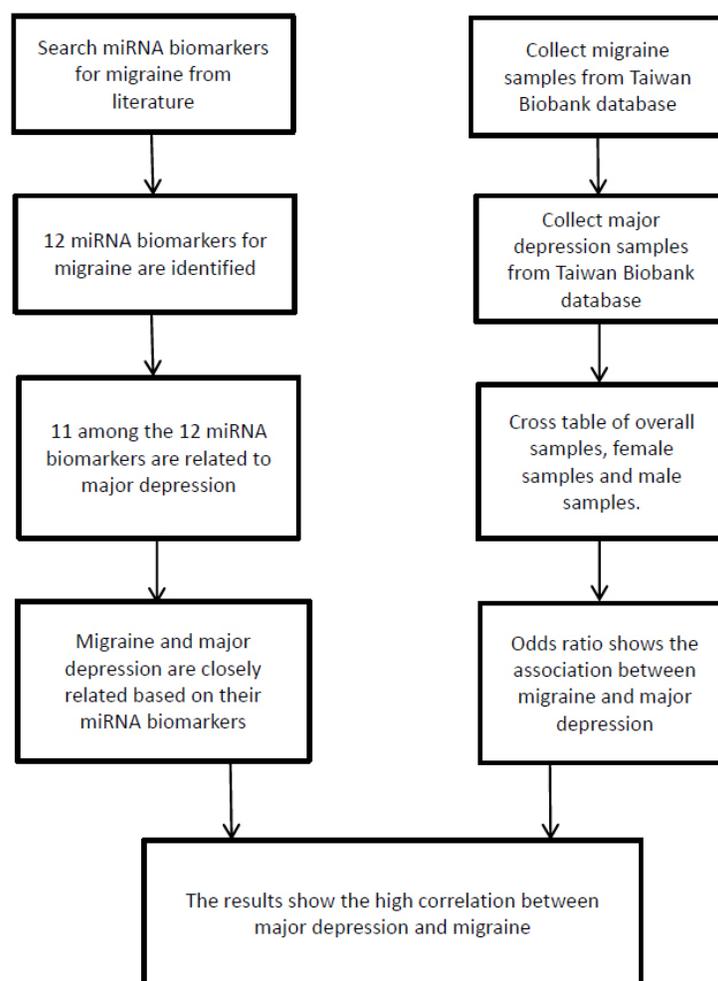A flowchart of the analyses is given in (Fig. **1**).

Fig. (1). The flow chart of miRNA analysis and Taiwan Biobank data analysis.

4. DISCUSSION

We searched the literature to find 12 miRNA biomarkers of migraine, of which 11 were relevant to MD. This indicates a high relationship between migraine and MD based on the miRNA biomarkers. In addition, hormone change was shown to be associated with an increased risk of developing depression [60]. On the other hand, serum hormone (estrogen) levels were higher in breast cancer cases than controls [61]. These studies revealed that there was an association between MD and breast cancer.

It was noted that the 12 migraine miRNA biomarkers are also related to breast cancer, which provides further evidence to link migraine and MD. For example, miR-590-5p inhibited breast cancer cell stemness by targeting SOX2, which indicated that miR-590-5p

might be developed to be a useful breast cancer treatment [62]. miR-34a collaborated in breast tumor suppression [63]. miR-382-5p played an oncogenic role in breast cancer initiation and progression in targeting and repressing RERG [62]. miR-30a-5p was a tumor suppressor in breast cancer through the inhibition of LDHA [64]. miR-375 targeted PAX6 and inhibited the viability, migration, and invasion of human breast cancer Michigan cancer foundation (MCF)-7 cells [65]. miR-27b-3p targeted CBLB/GRB2 in breast cancer cells that inhibited proliferation and potentially reversed the multi-chemoresistance of breast cancer cells [66].

In addition to miRNA analysis, the statistical analysis based on the large-scale epidemiologic data collected from TWB provides empirical evidence on the rela-

tionship between MD and migraine. The empirical association between MD and migraine seems to be gender-dependent: the statistical analysis based on the TWB sample reveals that the MD-migraine association is stronger in females than in males.

CONCLUSION

MD is one of the most ordinary mental disorders that is a comorbidity of many other illnesses. This study discusses the relationship between MD and migraine. Migraine is a prevalent neurovascular disease affecting many people worldwide. We explore their relationship based on their miRNA biomarkers and a cohort study based on TWB data. Eleven of the twelve migraine miRNA biomarkers are related to MD, which reveal the strong association between these two diseases. Also, the cohort study using TWB data showed a high correlation between these two diseases. Given the evidence-based on both molecular and epidemiological data, we suggest exploring the correlated underlying mechanism of these two diseases.

LIST OF ABBREVIATIONS

CSF   = Cerebro Spinal Fluid

CI   = Confidence Interval

GERD = Gastro Esophageal Reflux Disease

MD   = Major Depression

MCF   = Michigan Cancer Foundation

miRNA = microRNA

MS   = Multiple Sclerosis

OR   = Odds Ratio

PCR   = Polymerase Chain Reaction

SM   = Status Migrainosus

SLE   = Systemic Lupus Erythematosus

TWB   = Taiwan Biobank

AUTHOR CONTRIBUTIONS

Y.H.C and H.W. conceived and analyzed the data, and wrote the paper.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study has been approved by the Institutional Review Board of Academia Sinica (AS-IR-B01–17049). Written informed consent was obtained from all participants prior to the data collection.

HUMAN AND ANIMAL RIGHTS

No animals/humans were used for studies that are the basis of this research.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The Taiwan Biobank data and materials are available by application to The Taiwan Biobank Academia Sinica. Details about the data access to the Taiwan Biobank can be found at https://www.tw-biobank.org.tw/new_web_en/about-export.php,

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CONFLICTS OF INTEREST

The author declares no conflict of interest.

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