Anti-NMDA receptor encephalitis, human papillomavirus, and microRNA

Hsiuying Wang
Institute of Statistics, National Yang Ming Chiao Tung University, 300093, Hsinchu, Taiwan
wang@stat.nycu.edu.tw

Abstract

Background: Anti-N-methyl-d-aspartate (Anti-NMDA) receptor encephalitis is a rare autoimmune disease, which is caused by antibodies attacking NMDA receptors in the brain. Previous studies revealed that this disorder might be induced by vaccination. Vaccination is the most useful strategy to prevent human or animal infectious diseases. Although vaccines can produce immunity against diseases, at low risk, they may trigger serious adverse events. Anti-NMDA receptor encephalitis has been studied to be related to the H1N1 (influenza A virus subtype H1N1), tetanus/diphtheria/pertussis and polio vaccine, Japanese encephalitis, yellow fever, and coronavirus disease 2019 (COVID-19) vaccination. Several cases have been reported that anti-NMDA receptor encephalitis could also be triggered by the human papillomavirus (HPV) vaccine. However, there is a lack of studies to investigate the underlying mechanism.

Methods: This study discussed the potential association between anti-NMDA receptor encephalitis and HPV vaccination in terms of their microRNA (miRNA) biomarkers. Phylogenetic tree and distance similarity analyses are used to explore the relationship between their miRNA biomarkers.

Results: The analysis shows a higher degree of similarity between miRNA biomarkers linked to HPV and those associated with anti-NMDA receptor encephalitis or its related vaccines when compared to the overall miRNAs. It indicates that while the risk of HPV triggering anti-NMDA receptor encephalitis is low, a connection between anti-NMDA receptor encephalitis and HPV vaccination cannot be ruled out.

Conclusion: While the risk of HPV vaccination triggering Anti-NMDA receptor encephalitis appears to be low, the results of this study do not rule out a potential association. This finding suggests that in cases where individuals receiving HPV vaccination experience psychiatric or neurological symptoms, it should be considered to diagnose anti-NMDA receptor encephalitis, given the exclusion of other possible complications.

Keywords: anti-NMDA receptor encephalitis, biomarkers, human papillomavirus, microRNA, phylogenetic tree, tumor, vaccine

1. Introduction

Anti-N-methyl-d-aspartate (Anti-NMDA) receptor encephalitis is an acute autoimmune disorder that develops both neurological symptoms and psychiatric symptoms, including hallucination, cognitive disturbance, epilepsy, movement disorder, and impaired consciousness. Dalmau and his colleagues first described this disease in 2007 [1], but many cases or some extreme cases might date back to before 2007 [2, 3]. This disease may be misdiagnosed at the early stage as a psychosis disease because of primary psychiatric symptoms. The misdiagnosis may delay appropriate therapeutic intervention. This disease is more common in women than in men. The causes of some patients are associated with tumors, especially ovarian teratomas, and these patients can be treated with tumor resection. Most patients with anti-NMDA receptor encephalitis respond to immunotherapy. A treatment strategy using at least two of these therapies might have higher efficacy rates than treatment with only a single form of therapy [4], and treatment efficacy may depend on gender [5]. Early treatment with proteasome inhibitor bortezomib appears safe in anti-NMDA receptor encephalitis [6].

The pathology of this disease is an autoimmunity reaction that anti-NMDA antibodies attack patients' brains. Tumors might induce anti-NMDA receptor immune responses due to cross-reactivity with NMDA receptors in teratomas containing brain cells [7]. Ovarian teratomas could trigger anti-NMDA receptor encephalitis [8, 9], and other tumors including neuroendocrine tumors, mediastinal teratomas, testicular teratomas, and small-cell lung carcinoma have been reported to be associated with anti-NMDA antibodies [10-13].

In addition to tumors, other types of encephalitis may trigger anti-NMDA receptor encephalitis. Japanese encephalitis (JE) and herpes simplex virus (HSV) encephalitis might induce anti-NMDA receptor encephalitis [13]. Three patients who had confirmed JE were examined to have positive anti-NMDA receptor immunoglobulin G in their cerebrospinal fluid (CSF) [14]. Anti-NMDA receptor encephalitis has been reported to follow HSV encephalitis with seroconversion rates of up to 30% [15]. In addition, autoimmune diseases might be triggered by immunity induced by vaccination [16]. Several anti-NMDA receptor encephalitis cases have been reported to be associated with vaccination. A two-year-old girl developed anti-NMDA receptor encephalitis following a second dose of JE vaccination [17]. Several patients developed anti-NMDA receptor encephalitis following H1N1 influenza (influenza A virus subtype H1N1), or diphtheria/pertussis/tetanus/poliomyelitis vaccination [18, 19]. A 22-year-old female patient developed anti-NMDA receptor encephalitis after receiving a booster vaccination against diphtheria/pertussis/tetanus/poliomyelitis [20]. Recently, it was reported that stress might cause this disease, and stress management may prevent relapse [21]. New evidence showed that immunosuppressive therapy after liver transplantation could induce anti-NMDA receptor encephalitis [22]. The coronavirus disease 2019 (COVID-19) pandemic is a serious health crisis caused by the spread of the SARS-CoV-2 virus [23, 24]. COVID-19 vaccination or infection has been reported to be related to anti-NMDA receptor encephalitis [25]. Anti-NMDA receptor encephalitis has been reported to be associated with COVID-19 in a 7-year-old boy [26]. A 21-year-old woman with a history of COVID-19 was diagnosed with anti-NMDA receptor encephalitis [27]. A 53-year-old woman was accompanied by SARS-CoV-2 infection during an anti-NMDA receptor encephalitis episode [28]. A 33-year-old woman developed acute anti-NMDA receptor encephalitis following COVID-19 vaccination [29]. A 20-year-old female presented with abnormal behavior following the first dose of the BNT162b2 COVID-19 m-RNA vaccine, and anti-NMDA receptor antibodies were identified in both her serum and CSF [27].

In addition to these vaccines, cases of papillomavirus (HPV) vaccination triggering anti-NMDA receptor encephalitis have been reported, but the underlying mechanism has not been explored [30, 31]. HPV vaccination prevents infections with HPV, which can cause cervical cancer (CC). CC is one of the most common cancers threatening women's health that develops in a woman's cervix. High-risk subtypes of HPV were the cause of CC in most cases [32]. Persistent infection of high-risk HPV might induce CC and many other cancers [33]. Since the vaccine is expected to be less effective after an individual has been exposed to HPV, the vaccination is recommended before the age of

sexual debut. The World Health Organization (WHO) recommended vaccination against HPV for girls aged 9–14 [34].

Cases of adverse events related to HPV vaccination including chronic fatigue syndrome, postural orthostatic tachycardia syndrome (POTS), orthostatic intolerance, and complex regional pain syndrome have been reported [35-38]. Compared to these adverse events, only a few studies reported anti-NMDA receptor encephalitis cases that were associated with HPV vaccination. A woman with postural tachycardia syndrome after HPV vaccination tested positive for anti-NMDA receptor antibodies [30]. A study investigated the vaccines that might trigger anti-NMDA receptor encephalitis by searching VigiBase (a WHO database) up to 31 December 2021 [31]. It showed that the HPV vaccine (15.7%) and diphtheria/pertussis/tetanus/poliomyelitis vaccine (15.7%) were most commonly suspected of being associated with anti-NMDA receptor encephalitis, followed by the influenza vaccine (13.7%). Since cases of HPV vaccination triggering anti-NMDA receptor encephalitis have been reported, this study investigates the underlying mechanism from a molecular perspective. The method is based on the phylogenetic analyses of microRNA (miRNA) biomarkers.

miRNAs are single-stranded non-coding RNAs, approximately 22-24 nucleotides in length, that play important roles in the regulation of gene expression, cell proliferation, and apoptosis [39]. In cancer development, miRNAs function as tumor suppressors or oncogenes by targeting specific genes [40]. In addition to cancer, miRNA also may contribute to neurological diseases and inflammation in the brain [41] and other diseases [42-45]. Different diseases share many common miRNA biomarkers such as major depression, aging diseases, and autoimmune diseases [46-50]. miRNA biomarkers have been used to explore the relationship between anti-NMDA receptor encephalitis and vaccination (or tumors) [13, 17, 25, 51, 52].

2. Materials and Methods

2.1 MicroRNA biomarker

A literature search was conducted to identify miRNA biomarkers of HPV. The Web of Science, PubMed, and Google Scholar databases were used to find relevant papers by performing a systematic search using the following terms “microRNA” and “HPV” or “miRNA” and “HPV”. Some of the results are presented in Table 1. Not all of the searched miRNA biomarkers for HPV are considered in this study. One of the reasons is that the number of searched miRNA biomarkers is much larger than those used for other vaccines or anti-NMDA receptor encephalitis. If all of the searched biomarkers are used, the analysis result may be biased due to the unbalanced problem.

Two miRNA databases miRBase (https://www.mirbase.org) [53] and MirGeneDB (https://mirgenedb.org/) [54, 55] are used to obtain miRNA sequences. The miRNA IDs of these miRNA biomarkers of these two databases are provided in Tables 1 and 2.

Table 1. miRNA biomarkers for HPV

miRNA miRBase ID	MirGeneDB ID	Reference
miR-29a	Hsa-Mir-29-P2b	[56, 57]
miR-375	Hsa-Mir-375	[56, 58-60]
miR-195	Hsa-Mir-15-P2d	[56, 61]
miR-99a	Hsa-Mir-10-P2c	[56, 62]
miR-155	Hsa-Mir-155	[56, 63]
miR-92a	-	[56, 64]
miR-15b	Hsa-Mir-15-P1b	[65, 66]
miR-16	-	[65, 67]
miR-193b	Hsa-Mir-193-P1a	[65, 68]
miR-203	Hsa-Mir-203-v1 Hsa-Mir-203-v2	[65, 69, 70]
miR-497	Hsa-Mir-15-P1d	[61, 71]
miR-363	Hsa-Mir-92-P2c	[61, 72]
miR-143	Hsa-Mir-143	[61, 73]
miR-145	Hsa-Mir-145	[61, 73]
miR-424	Hsa-Mir-15-P1c	[60, 74]
miR-139a	-	[75]

The 16 miRNAs presented in Table 1 are used as miRNA biomarkers in this study. The 6 miRNAs, miR-375, miR-29a, miR-99a, miR-155, miR-92a, and miR-195 were

validated to be related to HPV-infected cells using the real-time reverse transcription polymerase chain reaction, and miR-29a was shown to be most highly enriched by a miRNA-mRNA regulatory network [56]. miR-375 expression was significantly downregulated in CC [58]. The overexpression of miR-375 significantly induced apoptosis in HPV-18(+) CC cells [59]. miRNA expression profiles were studied in HPV- negative and HPV- positive head and neck squamous cell carcinoma (HNSCC) against cervical squamous cell carcinoma (CSCC), and miR-195, miR-497, miR-363, miR-143, and miR-145 were significantly different expressed [61]. High-risk HPV can encode E6 and E7 proteins which are the oncogenic drivers. miR-15b, miR-16, miR-193b, and miR-203a were consistently upregulated or downregulated in human foreskin keratinocytes with stable expression of HPV16 E6/E7 compared with a control vector [65]. miR-424 played an important role in the regulation of HPV replication [74]. miR-139-3p targeted high-risk HPV-16 oncogenic proteins and activate major tumor suppressor proteins (p53, p21, and p16) [75].

The miRNA biomarkers of anti-NMDA receptor encephalitis were studied [51]. The miRNA biomarkers of other vaccines related to anti-NMDA receptor encephalitis were discussed in Wang (2017)[17] (Table 4). There are several common miRNAs in Tables 1 and 2 including miR-29a, miR-145, miR-15b, and miR-155.

Table 2. miRNA biomarkers for H1N1, pertussis, poliomyelitis, herpes simplex virus, Japanese encephalitis virus, COVID-19, and anti-NMDA receptor encephalitis in the reference [17, 25]

Vaccine or encephalitis	**miRBase ID**	**MirGeneDB ID**
H1N1	miR-323, miR-491, miR-654, miR-10a, let-7c, let-7f, miR-31, miR-29a, miR-148a, miR-146a	Hsa-Mir-491, Hsa-Mir-154-P23, Hsa-Mir-10-P1c-v1, Hsa-Mir-10-P1c-v2, Hsa-Mir-31, Hsa-Mir-29-P2b, Hsa-Mir-148-P1, Hsa-Mir-146-P4
pertussis	miR-202, miR-342, miR-206, miR-487b, miR-576	Hsa-Mir-202, Hsa-Mir-342, Hsa-Mir-1-P2, Hsa-Mir-154-P17, Hsa-Mir-576
poliomyelitis	miR-555	-

herpes simplex virus	miR-145, miR-101	Hsa-Mir-145, Hsa-Mir-101-P1-v1, Hsa-Mir-101-P1-v2, Hsa-Mir-101-P2-v1, Hsa-Mir-101-P2-v2
Japanese encephalitis virus	miR-19b-3p, miR-33a-5p, miR-155, miR-29b, miR-146a	Hsa-Mir-155, Hsa-Mir-146-P4
COVID-19	miR-16-2, miR-6501, miR-618, miR-183, miR-627, miR-144, miR-15a, miR-15b, miR548c, miR-548d, miR-409, miR-30b, miR-505, miR-4485, miR-483, miR-6891, miR-4284, miR-4463, miR-12136, miR-107, miR-125b, miR-29b, miR-299, miR-501, miR-181, miR-4745, let-7a, miR-374a, miR-194, miR-4454, miR-135b, miR-23b, let-7f-1, miR-429, miR-5701, miR-450b, miR-7-1, miR-26b, miR-23c, miR-374c, miR-374b, miR-26a, miR-365a, miR-365b, miR-940, miR-362, miR-1275, miR-1296, miR-548d, miR-16-2, miR-155, miR-126, miR-15b, miR-142, miR-146a, miR-21,	Hsa-Mir-15-P1a Hsa-Mir-15-P1b Hsa-Mir-154-P36 Hsa-Mir-30-P2a Hsa-Mir-483 Hsa-Mir-103-P1 Hsa-Mir-362-P3 Hsa-Mir-374-P1 Hsa-Mir-135-P4 Hsa-Mir-23-P2 Hsa-Mir-8-P3a Hsa-Mir-450-P3 Hsa-Mir-7-P2 Hsa-Mir-26-P2 Hsa-Mir-374-P2 Hsa-Mir-193-P2a Hsa-Mir-193-P2b Hsa-Mir-362-P1 Hsa-Mir-1296 Hsa-Mir-155 Hsa-Mir-146-P4 Hsa-Mir-21, Hsa-Mir-505-v1 Hsa-Mir-505-v2, Hsa-Mir-154-P2-v1, Hsa-Mir-154-P2-v2, Hsa-Mir-126-P2-v1 Hsa-Mir-126-P2-v2 Hsa-Mir-126-P2-v3, Hsa-Mir-142-P1-v1 Hsa-Mir-142-P1-v2 Hsa-Mir-142-P1-v3 Hsa-Mir-142-P1-v4,

Anti-NMDA receptor encephalitis	let-7a, let-7b, let-7d, let-7f	Hsa-Let-7-P2a1 Hsa-Let-7-P2b2, Hsa-Let-7-P2c1 Hsa-Let-7-P2b1

2.2 Phylogenetic tree

The phylogenetic tree analysis was a useful tool in the miRNA study [76-80] and has been successfully used in exploring the association between anti-NMDA receptor encephalitis and vaccination or other diseases [13, 17, 25]. The procedure of using phylogenetic tree analyses to explore the disease association has been proposed [81].
To construct the phylogenetic trees of the miRNA biomarkers, pre-miRNA stem-loop sequences of the miRNA biomarkers in Tables 1 and 2 were obtained from miRBase and MirGeneDB databases.

2.3 Similarity analysis

In addition to using the phylogenetic tree method based on the pre-miRNA sequences to discuss the relationship of the miRNA biomarkers, another approach useful method is using the similarity of these miRNA biomarkers based on the miRNA mature sequence. The pre-miRNA can provide more information about miRNAs, while the mature miRNA is the functional one that can target mRNAs. If the average distance of miRNA biomarkers of two diseases is relatively small compared with the average distance of all miRNAs, then the two diseases may have an association [82]. The distance distribution of miRNAs can be used to evaluate the similarity of miRNAs. Since the distance distribution of the mature miRNA sequences in MirGeneDB database has been derived [82], the similarity of miRNA biomarkers is examined based on the mature miRNA sequences from MirGeneDB database. The miRNA IDs of MirGeneDB corresponding to the miRNA IDs of MiRBase are provided in Tables 3 and 4. Since the number of miRNAs stored in MirGeneDB is less than that in MiRBase, not all miRNAs in miRBase have corresponding MirGeneDB IDs.

3. Results

The relationship between miRNA biomarkers of HPV and those of anti-NMDA receptor encephalitis is explored by the phylogenetic tree analysis and distance similarity analysis.

3.1 Phylogenetic Tree using miRBase database

Phylogenetic trees were constructed for miRNA biomarkers associated with HPV and anti-NMDA receptor encephalitis, as well as for some viruses related to anti-NMDA receptor encephalitis, including H1N1, JE virus, and HSV. First, the pre-miRNA stem-

loop sequences obtained from miRBase are used to construct the phylogenetic trees based on the Jukes-Cantor distance method and average method using Matlab software. The phylogenetic tree of miRNA biomarkers for HPV and anti-NMDA receptor encephalitis is plotted in Figure 1(a). The results show that the four anti-NMDA receptor encephalitis biomarkers are in a branch separated from HPV biomarkers. Since the miRNA biomarkers of HPV and anti-NMDA receptor encephalitis are not close, it might indicate a low risk of HPV triggering this disorder. Furthermore, the phylogenetic trees of miRNA biomarkers for HPV and several anti-NMDA receptor encephalitis-related vaccines or viruses including H1N1, JE, and HSV are plotted, respectively (Figure 1(b) and Figures 2). In these figures, the biomarkers of HPV and other biomarkers cannot be classified into two groups. As a result, despite the not strong association result from Figure 1(a), the relationship between anti-NMDA receptor encephalitis and HPV may not be excluded. It is worth noting that miR-375, a biomarker associated with HPV, appears in a separate branch in most of these figures, indicating that it is distinct from other miRNA biomarkers of HPV or other viruses. This suggests that miR-375 may be a valuable specific biomarker for HPV detection.

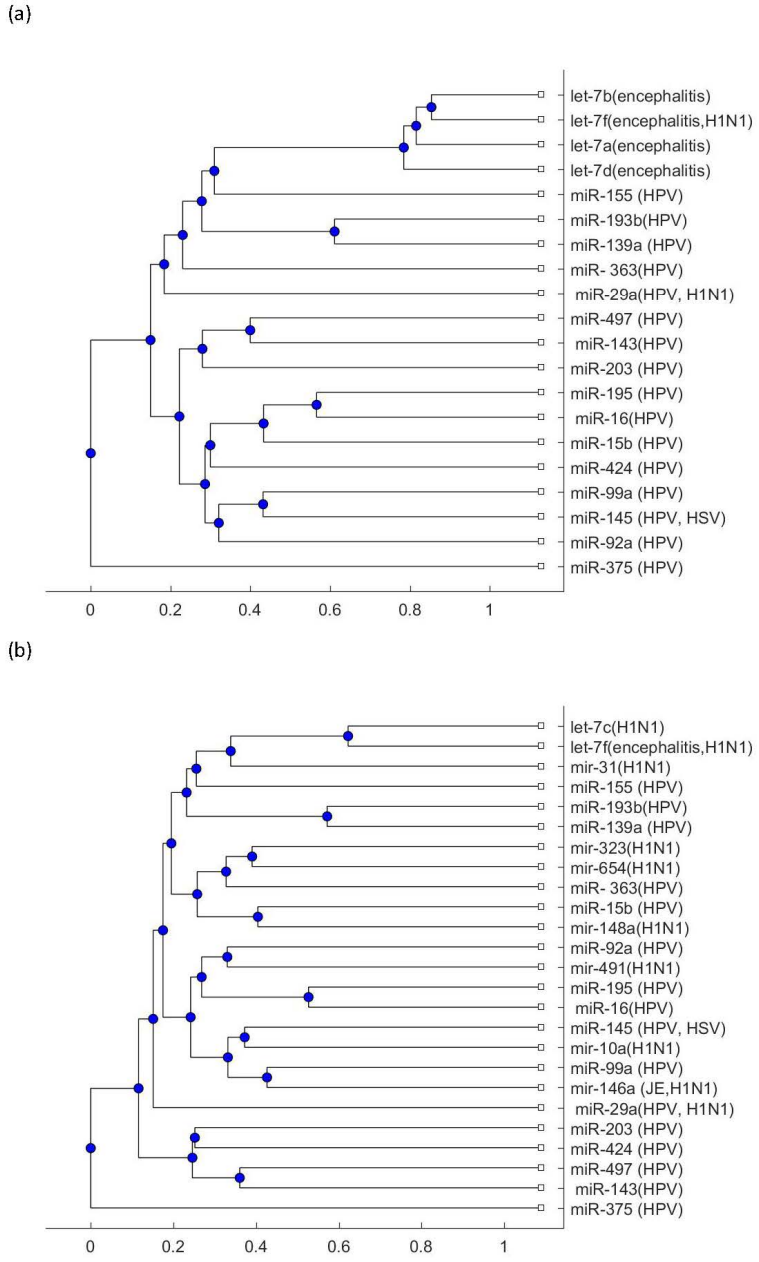

Figure 1. (a) The phylogenetic tree of miRNA biomarkers for HPV and anti-NMDA receptor encephalitis (miRBase data); (b) The phylogenetic tree of miRNA biomarkers for HPV and H1N1 (miRBase data)

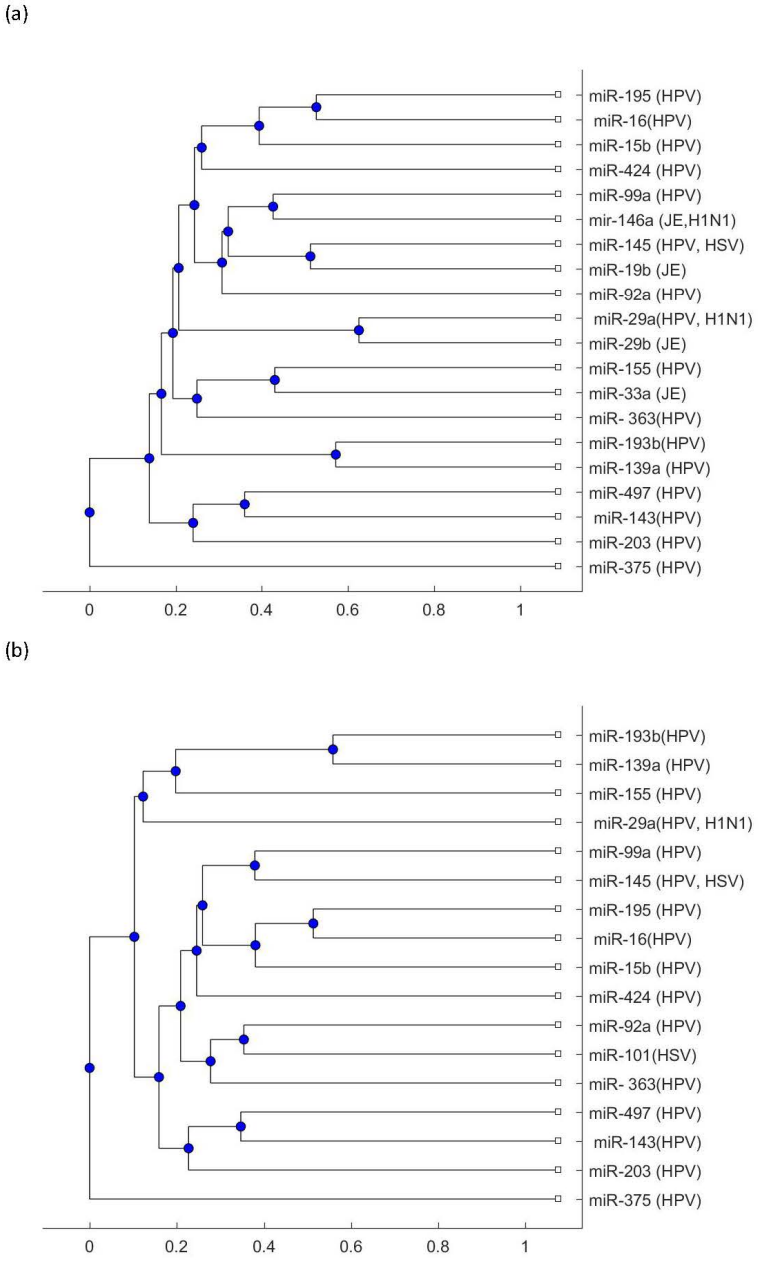

Figure 2. (a) The phylogenetic tree of miRNA biomarkers for HPV and JE (miRBase data) (b) The phylogenetic tree of miRNA biomarkers for HPV and herpes simplex virus (miRBase data)

3.2 Phylogenetic Tree using MirGeneDB Database

Next, the pre-miRNA stem-loop sequences obtained from MirGeneDB database are used to plot the phylogenetic trees. Figures 3 and 4 show a similar result to the result from miRBase database. In addition, miR-375 is also in a branch separated from other miRNAs. Therefore, according to the results from both miRBase and MirGeneDB databases, miR-375 is a specific biomarker for HPV that is worth further investigation.

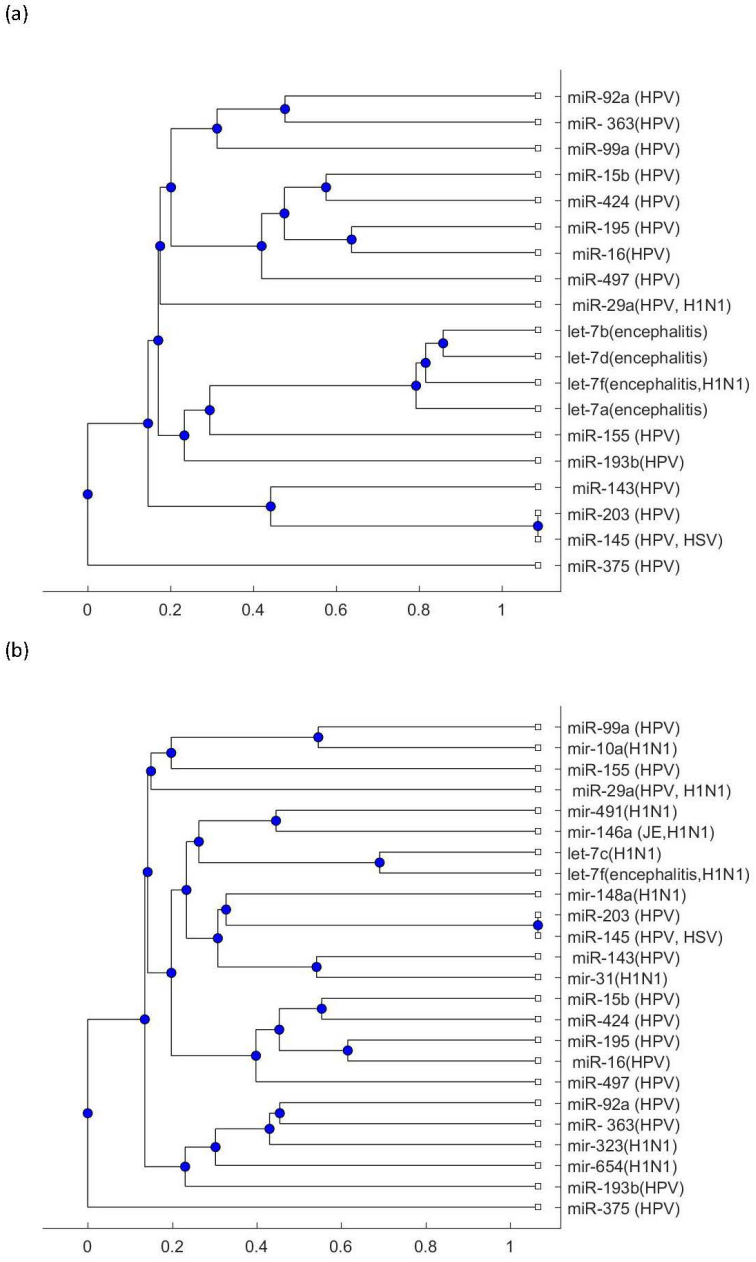

Figure 3. (a) The phylogenetic tree of miRNA biomarkers (MirGeneDB data) for HPV and anti-NMDA receptor encephalitis (MirGeneDB data); (b) the phylogenetic tree of miRNA biomarkers for HPV and H1N1 (MirGeneDB data)

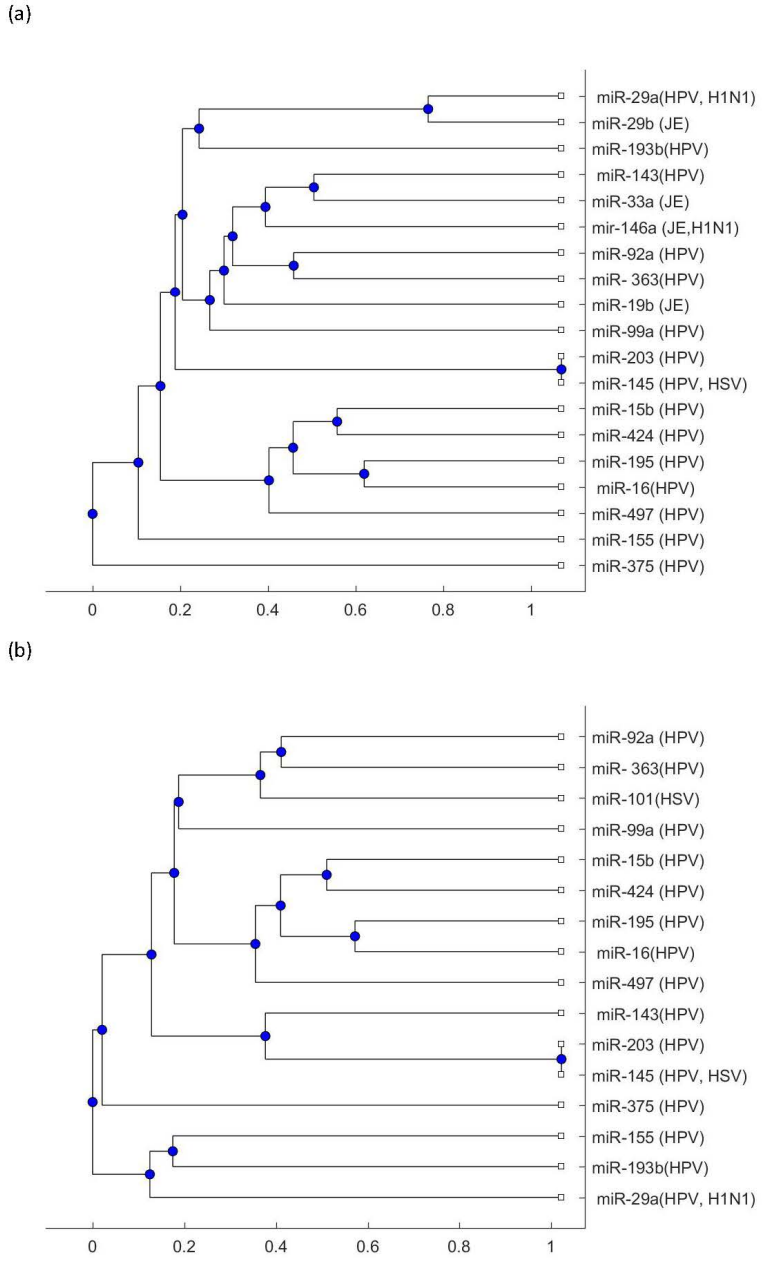

Figure 4. (a) The phylogenetic tree of miRNA biomarkers for HPV and JE (MirGeneDB data); (b) the phylogenetic tree of miRNA biomarkers for HPV and herpes simplex virus (MirGeneDB data)

3.3 The similarity of miRNA biomarkers

The phylogenetic tree analysis can provide a rough visualization to analyze the relationship of the miRNA biomarkers. A more depth analysis can be based on the miRNA distance distributions. A small average distance of the miRNA biomarkers for two diseases might indicate an association between these two diseases [82, 83]. More details are provided in the Materials and Methods section. Tables 3 and 4 show the average distances based on two distance models (Jukes-Cantor model and Kimura model) for the biomarkers of HPV alone, HPV and HIN1 together, HPV and pertussis together, HPV and HSV together, HPV and JE virus together, HPV and COVID-19 together, and HPV and anti-NMDA receptor encephalitis together, respectively. The case of HPV alone in Tables 3 and 4 calculates the pairwise distances of 14 miRNAs with MirGeneDB ID in Table 1. The case of HPV and HIN1 together calculates the pairwise distances of 21 miRNAs (the third row in Tables 1 and 2). There are 14 miRNAs for HPV and eight miRNAs for H1N1 in MirGeneDB, but HPV and H1N1 have a common biomarker miR-29a. Therefore, the pairwise distances of the 21 (14+8-1) miRNAs are calculated.

The corresponding percentiles of these average distances can be estimated using Table 2 and Table 4 of Wang (2022)[82]. The smaller the percentile, the more similar these miRNAs are. Tables 3 and 4 show that many of these percentiles are less than the 30 percentile. It indicates that they are relatively similar compared with the overall miRNAs. As a result, the miRNA biomarkers of HPV are relatively similar to those of anti-NMDA receptor encephalitis or those of vaccines related to this encephalitis. In conclusion, while the association between HPV and anti-NMDA receptor encephalitis is not strong, it cannot be completely ruled out based on the study of their miRNA biomarkers.

Table 3. The average distances of miRNA biomarkers and the corresponding percentiles based on Jukes-Cantor model

Vaccines or diseases	The average distance of miRNA pairwise distance	The percentile of the average distance
HPV	1.37745	27
HPV, H1N1	1.55726	39
HPV, pertussis	1.50918	37
HPV, herpes simplex virus	1.32532	24

HPV, Japanese encephalitis virus	1.41060	30
HPV, COVID-19	1.60469	42
HPV, Anti-NMDA receptor encephalitis	1.38898	28

Table 4. The average distances of miRNA biomarkers and the corresponding percentiles based on Kimura model

Vaccines or diseases	The average distance of miRNA pairwise distance	The percentile of the average distance
HPV	1.02880	19
HPV, H1N1	1.10861	21
HPV, pertussis	1.10968	21
HPV, herpes simplex virus	0.96933	14
HPV, Japanese encephalitis virus	1.04861	19
HPV, COVID-19	1.27224	38
HPV, Anti-NMDA receptor encephalitis	1.11596	22

4. Discussion

In this study, the relationship between miRNA biomarkers of HPV and miRNA biomarkers of anti-NMDA receptor encephalitis is investigated which is used to examine the association between HPV and anti-NMDA receptor encephalitis. miR-375 is the most distinct miRNA of HPV from the four biomarkers let-7a, let-7b, let-7d, and let-7f of the anti-NMDA receptor encephalitis (Figures 1-4), while miR-155 is the most similar miRNA biomarker of HPV to the four biomarkers of the anti-NMDA receptor encephalitis (Figure 1 and Figure 3). Figures 1-4 are plotted based on the distance of pre-miRNAs. The human pre-miRNA distance distribution has been derived as well as

the human mature distance distribution [83]. The average of the pre-miRNA pairwise distance of miR-375 to the four biomarkers let-7a, let-7b, let-7d, and let-7f of the anti-NMDA receptor encephalitis is 1.3008, which is in the 92nd percentile of the pre-miRNA distance distribution [83]. It indicates that miRNA-375 is very dissimilar to the miRNA biomarkers of anti-NMDA receptor encephalitis. The average of the pre-miRNA pairwise distances of miR-155 to the four biomarkers of anti-NMDA receptor encephalitis is 0.8184, which is the 16th percentile of the pre-miRNA distance distribution [83]. It indicates that miRNA-155 is very similar to the miRNA biomarkers of anti-NMDA receptor encephalitis.

This method identifies that miRNA-375 and miR-155 are the most dissimilar and the most similar miRNA biomarkers of HPV respectively, among the 16 HPV biomarkers compared to the miRNA biomarkers of anti-NMDA receptor encephalitis. The validity of these results can be confirmed by the related literature. Diabetes might be the most important disorder associated with miR-375, while immunity modulation might be the most important function related to miR-155. miR-375 was one of the most abundant miRNAs in the islets, and was required for normal glucose homeostasis [84, 85]. The immune system of diabetes patients might attack the β-cells in the pancreas, causing the pancreas to stop generating enough insulin to maintain normal levels of glucose in the blood [86]. Human cyclic adenosine monophosphate (cAMP) response element modulator (CREM) was a target gene of miR-375 and the interaction of CREM and miR-375 may account for β-cell regulation [87]. miR-155 might modulate immune cells including dendritic cells, B lymphocyte cells, and T lymphocyte cells, and contribute to autoimmune disease development [88]. miR-155 significantly impacted immune cells and the miR-155 expression increased after immune cell activation [89]. The proper and timely regulation of miR-155 expression was important for inducing an effective anti-virus immune response in many viral infections [90].

Anti-NMDA receptor encephalitis is an autoimmune disease that may be caused by infections, tumors, vaccination, or other unknown factors. It has been shown as a comorbidity of many diseases such as COVID-19 and tumors. So far, no evidence to show that any specific virus, vaccine, or disease is irrelevant to anti-NMDA receptor encephalitis. However, according to the literature search, diabetes may not be directly related to it, while the immune response is the main cause of anti-NMDA receptor encephalitis. The most dissimilar and similar biomarkers of HPV to this encephalitis are miR-375 and miR-155, respectively, which have been linked to diabetes and immunity modulation, respectively. As a result, this may indicate a rationale for using the similarity of miRNA biomarkers to explore the association between diseases.

HPV is a common sexually transmitted vector, and different types of HPV can infect the genital area of both men and women. HPV could also infect the lining of the mouth and throat, and was associated with CC, certain head and neck cancers, and cancers of the vulva, the vagina, the penis, and the anus [91]. Therefore, the HPV vaccination is an effective way to prevent these cancers. However, although the safety of the HPV vaccine has been investigated, more people have been concerned about the safety of the vaccine in recent years. Different adverse events following HPV vaccination have been reported [35-37]. The cases of POTS following HPV vaccination have raised concerns. Suspected adverse events after HPV vaccination include POTS, complex regional pain syndrome, headache, chronic fatigue syndrome, and orthostatic intolerance [38]. Vaccine-triggered, immune-mediated autonomic dysfunction was suggested for developing de novo post-HPV vaccination syndrome in genetically susceptible individuals [36]. A significantly different adverse event rate for HPV vaccination between the non-Hispanic White females and other race/ethnicity groups was found [37]. A 23-year-old woman was diagnosed with myasthenia gravis following HPV vaccination, presenting with binocular diplopia, dysarthria, ptosis, and dysphagia on the 3rd day after the second HPV vaccine administration [92]. After treatment, all symptoms had completely resolved at discharge. A 31-year-old female patient of systemic lupus erythematosus (SLE) onset after HPV vaccination was reported, and 11 similar cases were reviewed [93]. Since the suggested age (9 to 26 years) for HPV vaccination coincided with the age of high SLE incidence, the relationship between the SLE incidence and HPV vaccine might not be excluded [93].

The above-mentioned adverse events (myasthenia gravis and SLE) are autoimmune diseases as well as anti-NMDA receptor encephalitis. Most of the serious adverse events of HPV vaccination might be autoimmune disorders. Therefore, it is important to study how the immune system responds to vaccination, which can help understand the pathology by which these adverse events occur. In addition, it is worth mentioning that HPV can cause cancers, and anti-NMDA receptor encephalitis is associated with tumors. Ovarian teratomas were the most commonly reported anti-NMDA receptor encephalitis-associated tumor in females [94]. Testicular teratomas were reported to be associated with anti-NMDA receptor encephalitis in males [11]. HPV might induce CC and cancers of the vulva, the vagina, the penis, and the anus [95]. Both HPV and anti-NMDA receptor encephalitis have been associated with tumors or cancers of the male and female reproductive systems (Figure 5). This may shed light on investigating the mechanism of the association between HPV vaccination and anti-NMDA receptor encephalitis.

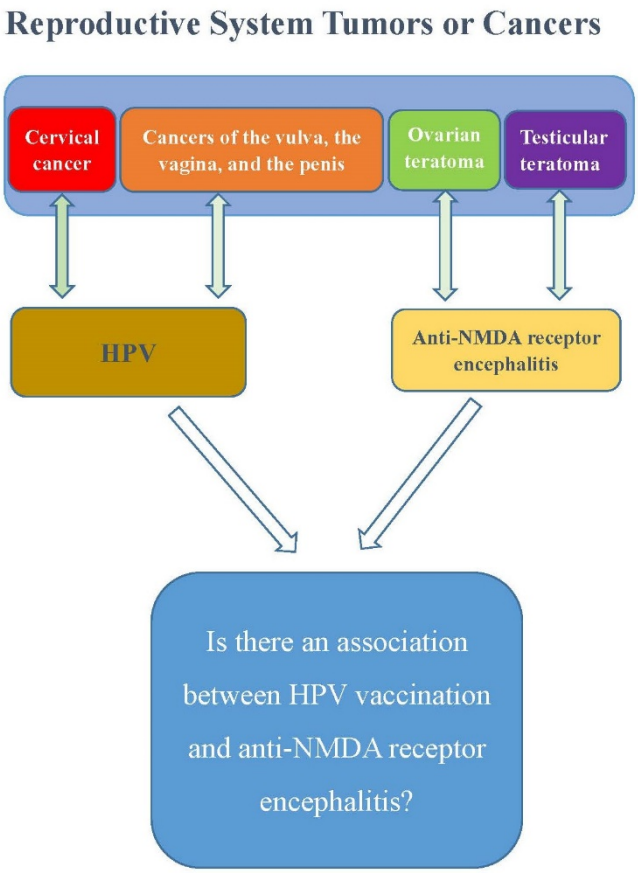

Figure 5. The involvement of reproductive system cancers or tumors may explain the association between HPV and anti-NMDA receptor encephalitis

5. Conclusion

This research is motivated by several cases of HPV vaccination triggering anti-NMDA receptor encephalitis reported in the literature. While vaccines, including the HPV vaccine, do not directly cause autoimmune diseases, they may trigger an autoimmune response or exacerbate existing autoimmune conditions in some individuals. The study explores the relationship between HPV and anti-NMDA receptor encephalitis using their miRNA biomarkers. This exploration aims to aid in understanding the underlying mechanism of how these biomarkers might be involved in the development of anti-NMDA receptor encephalitis following HPV vaccination. The results indicate that miRNA biomarkers for HPV, anti-NMDA receptor encephalitis, and related vaccines exhibit a relatively higher degree of similarity compared to overall miRNAs. The finding suggests that even though the probability of HPV causing anti-NMDA receptor encephalitis is limited, the potential association between anti-NMDA receptor

encephalitis and HPV vaccination should not be disregarded. Therefore, for individuals receiving HPV vaccination who develop psychiatric or neurological symptoms, a diagnosis of anti-NMDA receptor encephalitis should be considered if other complications are excluded.

Abbreviation list

Anti-NMDA receptor encephalitis: Anti-N-methyl-d-aspartate receptor encephalitis
CC: cervical cancer
COVID-19: Coronavirus disease 2019
CSCC: cervical squamous cell carcinoma
CSF: cerebrospinal fluid
H1N1: influenza A virus subtype H1N1
HNSCC: neck squamous cell carcinoma
HPV: papillomavirus
HSV: herpes simplex virus
JE: Japanese encephalitis
miRNA: microRNA
POTS: postural orthostatic tachycardia syndrome
SLE: systemic lupus erythematosus
WHO: World Health Organization

Funding

This work was supported by the Ministry of Science and Technology 111-2118-M-A49-001-MY2, Taiwan.

Conflicts of Interest

The author declares no conflict of interest.

References

[1] Dalmau, J.; Gleichman, A.J.; Hughes, E.G.; Rossi, J.E.; Peng, X.; Lai, M.; Dessain, S.K.; Rosenfeld, M.R.; Balice-Gordon, R.; Lynch, D.R., Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. *The Lancet Neurology,* **2008**, *7*, (12), 1091-1098.

[2] Sebire, G., In search of lost time from "Demonic Possession" to anti-N-methyl-D-aspartate receptor encephalitis. *Ann Neurol,* **2010**, *67*, (1), 141-142; author reply 142-143.

[3] Tam, J.; Zandi, M.S., The witchcraft of encephalitis in Salem. *J Neurol,* **2017**, *264*, (7), 1529-1531.

[4] Wang, H., Efficacies of treatments for anti-NMDA receptor encephalitis. *Frontiers in bioscience,* **2016**, *21*, 651-663.
[5] Wang, H., Anti-NMDA Receptor Encephalitis: Efficacy of Treatment for Male Patients and miRNA Biomarker. *Current medicinal chemistry,* **2018**.
[6] Turnbull, M.T.; Siegel, J.L.; Becker, T.L.; Stephens, A.J.; Lopez-Chiriboga, A.S.; Freeman, W.D., Early Bortezomib Therapy for Refractory Anti-NMDA Receptor Encephalitis. *Front Neurol,* **2020**, *11*, 188.
[7] Tuzun, E.; Zhou, L.; Baehring, J.M.; Bannykh, S.; Rosenfeld, M.R.; Dalmau, J., Evidence for antibody-mediated pathogenesis in anti-NMDAR encephalitis associated with ovarian teratoma. *Acta Neuropathol,* **2009**, *118*, (6), 737-743.
[8] Sanmaneechai, O.; Song, J.L.; Nevadunsky, N.; Moshé, S.L.; Overby, P.J., Anti-N-methyl-D-aspartate encephalitis with ovarian cystadenofibroma. *Pediatric neurology,* **2013**, *48*, (3), 232-235.
[9] Seki, M.; Suzuki, S.; Iizuka, T.; Shimizu, T.; Nihei, Y.; Suzuki, N.; Dalmau, J., Neurological response to early removal of ovarian teratoma in anti-NMDAR encephalitis. *Journal of Neurology, Neurosurgery & Psychiatry,* **2008**, *79*, (3), 324-326.
[10] Lim, E.W.; Yip, C.W., Anti-N-methyl-D-aspartate receptor encephalitis associated with hepatic neuroendocrine carcinoma: A case report. *Journal of Clinical Neuroscience,* **2017**, *41*, 70-72.
[11] Eker, A.; Saka, E.; Dalmau, J.; Kurne, A.; Bilen, C.; Ozen, H.; Ertoy, D.; Ouz, K.; Elibol, B., Testicular teratoma and anti-N-methyl-D-aspartate receptor-associated encephalitis. *Journal of Neurology, Neurosurgery & Psychiatry,* **2008**, *79*, (9), 1082-1083.
[12] Jeraiby, M.; Depincé-Berger, A.; Bossy, V.; Antoine, J.; Paul, S., A case of anti-NMDA receptor encephalitis in a woman with a NMDA-R+ small cell lung carcinoma (SCLC). *Clinical Immunology,* **2016**, *166*, 96-99.
[13] Wang, H., Phylogenetic Analysis to Explore the Association Between Anti-NMDA Receptor Encephalitis and Tumors Based on microRNA Biomarkers. *Biomolecules,* **2019**, *9*, (10), 572.
[14] Ma, J.; Zhang, T.; Jiang, L., Japanese encephalitis can trigger anti-N-methyl-D-aspartate receptor encephalitis. *Journal of neurology,* **2017**, *264*, (6), 1127-1131.
[15] Ewida, A.; Laxton, K.; Lou, A.; Suryadevara, N.; Sanders, A.; AAN Enterprises, **2019**.
[16] Steinman, L., Multiple sclerosis: a two-stage disease. *Nat Immunol,* **2001**, *2*, (9), 762-764.
[17] Wang, H., Anti-NMDA receptor encephalitis and vaccination. *International journal of molecular sciences,* **2017**, *18*, (1), 193.
[18] Hofmann, C.; Baur, M.-O.; Schroten, H., Anti-NMDA receptor encephalitis after

TdaP–IPV booster vaccination: cause or coincidence? *Journal of neurology,* **2011**, *258*, (3), 500-501.
[19] Dalmau, J.; Lancaster, E.; Martinez-Hernandez, E.; Rosenfeld, M.R.; Balice-Gordon, R., Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. *The Lancet Neurology,* **2011**, *10*, (1), 63-74.
[20] Endres, D.; Rauer, S.; Kern, W.; Venhoff, N.; Maier, S.J.; Runge, K.; Suss, P.; Feige, B.; Nickel, K.; Heidt, T.; Domschke, K.; Egger, K.; Pruss, H.; Meyer, P.T.; Tebartz van Elst, L., Psychiatric Presentation of Anti-NMDA Receptor Encephalitis. *Front Neurol,* **2019**, *10*, 1086.
[21] Obi, C.A.; Thompson, E.; Mordukhaev, L.; Khan, I.; Zhang, N.J. In *Baylor University Medical Center Proceedings*; Taylor & Francis, **2019**, pp 1-2.
[22] Konen, F.F.; Schwenkenbecher, P.; Jendretzky, K.F.; Hümmert, M.W.; Wegner, F.; Stangel, M.; Sühs, K.-W.; Skripuletz, T., Severe Anti-N-Methyl-D-Aspartate Receptor Encephalitis Under Immunosuppression After Liver Transplantation. *Frontiers in neurology,* **2019**, *10*.
[23] Chen, Y.H.; Wang, H., Exploring Diversity of COVID-19 Based on Substitution Distance. *Infect Drug Resist,* **2020**, *13*, 3887-3894.
[24] Wang, H., Tolerance limits for mixture-of-normal distributions with application to COVID-19 data. *Wiley Interdisciplinary Reviews: Computational Statistics*, e1611.
[25] Wang, H., COVID−19, Anti-NMDA Receptor Encephalitis and MicroRNA. *Frontiers in Immunology,* **2022**, 13:825103.
[26] Sarigecili, E.; Arslan, I.; Ucar, H.K.; Celik, U., Pediatric anti-NMDA receptor encephalitis associated with COVID-19. *Childs Nerv Syst,* **2021**, *37*, (12), 3919-3922.
[27] Lee, H.; Jeon, J.H.; Choi, H.; Koh, S.H.; Lee, K.Y.; Lee, Y.J.; Kwon, H.S., Anti-N-methyl-D-aspartate receptor encephalitis after coronavirus disease 2019: A case report and literature review. *Medicine (Baltimore),* **2022**, *101*, (35), e30464.
[28] McHattie, A.W.; Coebergh, J.; Khan, F.; Morgante, F., Palilalia as a prominent feature of anti-NMDA receptor encephalitis in a woman with COVID-19. *Journal of Neurology,* **2021**, *268*, (11), 3995-3997.
[29] Naz, A.; Mohamed, H.; Noha, S.; Abdallah, A.; Szolics, M.J.S.N., Acute Anti-N-Methyl D-Aspartate Receptor Encephalitis Following Covid-19 Vaccination. **2022**, *3*, (4), 143-145.
[30] Blitshteyn, S.; Brook, J., Postural tachycardia syndrome (POTS) with anti-NMDA receptor antibodies after human papillomavirus vaccination. *Immunol Res,* **2017**, *65*, (1), 282-284.
[31] Martin, S.; Azzouz, B.; Morel, A.; Trenque, T., Anti-NMDA receptor encephalitis and vaccination: A disproportionality analysis. *Front Pharmacol,* **2022**, *13*, 940780.
[32] Cohen, P.A.; Jhingran, A.; Oaknin, A.; Denny, L., Cervical cancer. *Lancet,* **2019**,

393, (10167), 169-182.
[33] Wang, R.; Pan, W.; Jin, L.; Huang, W.; Li, Y.; Wu, D.; Gao, C.; Ma, D.; Liao, S., Human papillomavirus vaccine against cervical cancer: Opportunity and challenge. *Cancer Lett,* **2020**, *471*, 88-102.
[34] Sundaram, N.; Voo, T.C.; Tam, C.C., Adolescent HPV vaccination: empowerment, equity and ethics. *Hum Vaccin Immunother,* **2020**, *16*, (8), 1835-1840.
[35] Arana, J.; Mba-Jonas, A.; Jankosky, C.; Lewis, P.; Moro, P.L.; Shimabukuro, T.T.; Cano, M., Reports of Postural Orthostatic Tachycardia Syndrome After Human Papillomavirus Vaccination in the Vaccine Adverse Event Reporting System. *J Adolesc Health,* **2017**, *61*, (5), 577-582.
[36] Blitshteyn, S.; Brinth, L.; Hendrickson, J.E.; Martinez-Lavin, M., Autonomic dysfunction and HPV immunization: an overview. *Immunol Res,* **2018**, *66*, (6), 744-754.
[37] Huang, J.; Du, J.; Duan, R.; Zhang, X.; Tao, C.; Chen, Y., Characterization of the Differential Adverse Event Rates by Race/Ethnicity Groups for HPV Vaccine by Integrating Data From Different Sources. *Front Pharmacol,* **2018**, *9*, 539.
[38] Ward, D.; Thorsen, N.M.; Frisch, M.; Valentiner-Branth, P.; Molbak, K.; Hviid, A., A cluster analysis of serious adverse event reports after human papillomavirus (HPV) vaccination in Danish girls and young women, September 2009 to August 2017. *Euro Surveill,* **2019**, *24*, (19).
[39] Hwang, H.W.; Mendell, J.T., MicroRNAs in cell proliferation, cell death, and tumorigenesis. *Br J Cancer,* **2006**, *94*, (6), 776-780.
[40] Peng, Y.; Croce, C.M., The role of MicroRNAs in human cancer. *Signal Transduct Target Ther,* **2016**, *1*, 15004.
[41] Karthikeyan, A.; Patnala, R.; Jadhav, S.P.; Eng-Ang, L.; Dheen, S.T., MicroRNAs: Key Players in Microglia and Astrocyte Mediated Inflammation in CNS Pathologies. *Current medicinal chemistry,* **2016**, *23*, (30), 3528-3546.
[42] Taguchi, Y.H.; Wang, H., Exploring microRNA Biomarker for Amyotrophic Lateral Sclerosis. *Int J Mol Sci,* **2018**, *19*, (5).
[43] Taguchi, Y.H.; Wang, H., Exploring MicroRNA Biomarkers for Parkinson's Disease from mRNA Expression Profiles. *Cells,* **2018**, *7*, (12).
[44] Takuse, Y.; Watanabe, M.; Inoue, N.; Ozaki, R.; Ohtsu, H.; Saeki, M.; Katsumata, Y.; Hidaka, Y.; Iwatani, Y., Association of IL-10-Regulating MicroRNAs in Peripheral Blood Mononuclear Cells with the Pathogenesis of Autoimmune Thyroid Disease. *Immunol Invest,* **2017**, *46*, (6), 590-602.
[45] Panebianco, V.; Paci, P.; Pecoraro, M.; Conte, F.; Carnicelli, G.; Besharat, Z.M.; Catanzaro, G.; Splendiani, E.; Sciarra, A.; Farina, L.; Catalano, C.; Ferretti, E., Network Analysis Integrating microRNA Expression Profiling with MRI Biomarkers and Clinical

Data for Prostate Cancer Early Detection: A Proof of Concept Study. *Biomedicines,* **2021**, *9*, (10).
[46] Wang, H., MicroRNAs, Multiple Sclerosis, and Depression. *Int J Mol Sci,* **2021**, *22*, (15).
[47] Niwald, M.; Migdalska-Sek, M.; Brzezianska-Lasota, E.; Miller, E., Evaluation of Selected MicroRNAs Expression in Remission Phase of Multiple Sclerosis and Their Potential Link to Cognition, Depression, and Disability. *J Mol Neurosci,* **2017**, *63*, (3-4), 275-282.
[48] Wang, H., MicroRNAs, Parkinson's Disease, and Diabetes Mellitus. *Int J Mol Sci,* **2021**, *22*, (6).
[49] Chen, Y.H.; Wang, H.Y., The Association between Migraine and Depression based on miRNA Biomarkers and Cohort Studies. *Current medicinal chemistry,* **2021**, *28*, (27), 5648-5656.
[50] Chen, Y.-H.; Wang, H., The association between depression and gastroesophageal reflux based on phylogenetic analysis of miRNA biomarkers. *Current medicinal chemistry,* **2020**, *27*, (38), 6536-6547.
[51] Zhang, J.; Xu, X.; Zhao, S.; Gong, Z.; Liu, P.; Guan, W.; He, X.; Wang, T.; Peng, T.; Teng, J.; Jia, Y., The Expression and Significance of the Plasma Let-7 Family in Anti-N-methyl-D-aspartate Receptor Encephalitis. *J Mol Neurosci,* **2015**, *56*, (3), 531-539.
[52] Wang, H., Anti-NMDA Receptor Encephalitis, Vaccination and Virus. *Current Pharmaceutical Design,* **2019**.
[53] Kozomara, A.; Birgaoanu, M.; Griffiths-Jones, S., miRBase: from microRNA sequences to function. *Nucleic Acids Res,* **2019**, *47*, (D1), D155-D162.
[54] Fromm, B.; Billipp, T.; Peck, L.E.; Johansen, M.; Tarver, J.E.; King, B.L.; Newcomb, J.M.; Sempere, L.F.; Flatmark, K.; Hovig, E.; Peterson, K.J., A Uniform System for the Annotation of Vertebrate microRNA Genes and the Evolution of the Human microRNAome. *Annu Rev Genet,* **2015**, *49*, 213-242.
[55] Fromm, B.; Domanska, D.; Hoye, E.; Ovchinnikov, V.; Kang, W.; Aparicio-Puerta, E.; Johansen, M.; Flatmark, K.; Mathelier, A.; Hovig, E.; Hackenberg, M.; Friedlander, M.R.; Peterson, K.J., MirGeneDB 2.0: the metazoan microRNA complement. *Nucleic Acids Res,* **2020**, *48*, (D1), D132-D141.
[56] Li, Y.; Wang, F.; Xu, J.; Ye, F.; Shen, Y.; Zhou, J.; Lu, W.; Wan, X.; Ma, D.; Xie, X., Progressive miRNA expression profiles in cervical carcinogenesis and identification of HPV-related target genes for miR-29. *The Journal of pathology,* **2011**, *224*, (4), 484-495.
[57] Zamani, S.; Hosseini, S.M.; Sohrabi, A., miR-21 and miR29-a: Potential Molecular Biomarkers for HPV Genotypes and Cervical Cancer Detection. *Microrna,* **2020**, *9*, (4), 271-275.

[58] Jayamohan, S.; Kannan, M.; Moorthi, R.K.; Rajasekaran, N.; Jung, H.S.; Shin, Y.K.; Arockiam, A.J.V., Dysregulation of miR-375/AEG-1 axis by Human Papillomavirus 16/18-E6/E7 Promotes Cellular Proliferation, Migration and Invasion in Cervical Cancer. *Frontiers in oncology,* **2019**, *9*, 847.
[59] Wu, S.; Chen, H., Anti-Condyloma acuminata mechanism of microRNAs-375 modulates HPV in cervical cancer cells via the UBE3A and IGF-1R pathway. *Oncology letters,* **2018**, *16*, (3), 3241-3247.
[60] Tian, Q.F.; Li, Y.; Wang, F.F.; Li, Y.; Xu, J.F.; Shen, Y.M.; Ye, F.; Wang, X.Y.; Cheng, X.D.; Chen, Y.X.; Wan, X.Y.; Lu, W.G.; Xie, X., MicroRNA Detection in Cervical Exfoliated Cells as a Triage for Human Papillomavirus-Positive Women. *Jnci-J Natl Cancer I,* **2014**, *106*, (9).
[61] Lajer, C.; Garnaes, E.; Friis-Hansen, L.; Norrild, B.; Therkildsen, M.H.; Glud, M.; Rossing, M.; Lajer, H.; Svane, D.; Skotte, L., The role of miRNAs in human papilloma virus (HPV)-associated cancers: bridging between HPV-related head and neck cancer and cervical cancer. *British journal of cancer,* **2012**, *106*, (9), 1526.
[62] Zhang, Q.; Chen, Y.; Hu, S.Q.; Pu, Y.M.; Zhang, K.; Wang, Y.X., A HPV16-related prognostic indicator for head and neck squamous cell carcinoma. *Ann Transl Med,* **2020**, *8*, (22), 1492.
[63] Chen, Y.Z.; Wang, J.W.; Meng, F.C.; Yang, P.; Zhang, X.G.; Wu, H.Z., LncRNATCF7 up-regulates DNMT1 mediated by HPV-18 E6 and regulates biological behavior of cervical cancer cells by inhibiting miR-155. *Eur Rev Med Pharmacol Sci,* **2019**, *23*, (20), 8779-8787.
[64] Wang, X.; Wang, H.K.; Li, Y.; Hafner, M.; Banerjee, N.S.; Tang, S.; Briskin, D.; Meyers, C.; Chow, L.T.; Xie, X.; Tuschl, T.; Zheng, Z.M., microRNAs are biomarkers of oncogenic human papillomavirus infections. *Proc Natl Acad Sci U S A,* **2014**, *111*, (11), 4262-4267.
[65] Harden, M.E.; Prasad, N.; Griffiths, A.; Munger, K., Modulation of microRNA-mRNA target pairs by human papillomavirus 16 oncoproteins. *MBio,* **2017**, *8*, (1), e02170-02116.
[66] Ocadiz-Delgado, R.; Cruz-Colin, J.L.; Alvarez-Rios, E.; Torres-Carrillo, A.; Hernandez-Mendoza, K.; Conde-Perezprina, J.C.; Dominguez-Gomez, G.I.; Garcia-Villa, E.; Lambert, P.F.; Gariglio, P., Expression of miR-34a and miR-15b during the progression of cervical cancer in a murine model expressing the HPV16 E7 oncoprotein. *J Physiol Biochem,* **2021**, *77*, (4), 547-555.
[67] Zubillaga-Guerrero, M.I.; Illades-Aguiar, B.; Flores-Alfaro, E.; Castro-Coronel, Y.; Jimenez-Wences, H.; Patino, E.I.L.B.; Perez, K.I.G.; Alarcon-Romero, L.D., An increase of microRNA-16-1 is associated with the high proliferation of squamous intraepithelial lesions in the presence of the integrated state of HR-HPV in liquid

cytology samples. *Oncology letters,* **2020**, *20*, (4).
[68] Xu, M.; Huseinovic, A.; Jaspers, A.; Yuan, L.; Steenbergen, R.D., Downregulation of miR-193a/b-3p during HPV-induced cervical carcinogenesis contributes to anchorage-independent growth through PI3K/AKT pathway regulators. *Journal of Medical Virology,* **2023**.
[69] Wang, Y.Y.; Xu, B.; Shen, X.Y.; Sun, L.N., Diagnostic value of miR-153 and miR-203 in patients with cervical cancer and their correlation with human papillomavirus infection. *Am J Transl Res,* **2021**, *13*, (8), 9736-9742.
[70] Marthaler, A.M.; Podgorska, M.; Feld, P.; Fingerle, A.; Knerr-Rupp, K.; Grasser, F.; Smola, H.; Roemer, K.; Ebert, E.; Kim, Y.J.; Bohle, R.M.; Muller, C.S.L.; Reichrath, J.; Vogt, T.; Malejczyk, M.; Majewski, S.; Smola, S., Identification of C/EBP alpha as a novel target of the HPV8 E6 protein regulating miR-203 in human keratinocytes. *Plos Pathog,* **2017**, *13*, (6).
[71] Luo, M.; Shen, D.X.; Zhou, X.N.; Chen, X.D.; Wang, W., MicroRNA-497 is a potential prognostic marker in human cervical cancer and functions as a tumor suppressor by targeting the insulin-like growth factor 1 receptor. *Surgery,* **2013**, *153*, (6), 836-847.
[72] Chapman, B.V.; Wald, A.I.; Akhtar, P.; Munko, A.C.; Xu, J.J.; Gibson, S.P.; Grandis, J.R.; Ferris, R.L.; Khan, S.A., MicroRNA-363 targets myosin 1B to reduce cellular migration in head and neck cancer. *Bmc Cancer,* **2015**, *15*.
[73] Liu, X.Y.; Zhang, Y.; Wang, S.; Liu, G.Y.; Ruan, L.M., Loss of miR-143 and miR-145 in condyloma acuminatum promotes cellular proliferation and inhibits apoptosis by targeting NRAS. *Roy Soc Open Sci,* **2018**, *5*, (8).
[74] Hong, S.; Cheng, S.; Songock, W.; Bodily, J.; Laimins, L.A., Suppression of microRNA 424 levels by human papillomaviruses is necessary for differentiation-dependent genome amplification. *Journal of virology,* **2017**, *91*, (24), e01712-01717.
[75] Sannigrahi, M.K.; Sharma, R.; Singh, V.; Panda, N.K.; Rattan, V.; Khullar, M., Role of host miRNA hsa-mir-139-3p in hpv-16–induced carcinomas. *Clinical cancer research,* **2017**, *23*, (14), 3884-3895.
[76] Graur, D.; Li, W.-H. *Fundamentals of molecular evolution*. 2nd ed. Sinauer: Sunderland, Ma., **2000**.
[77] Ma, Y.J.; Yang, J.; Fan, X.L.; Zhao, H.B.; Hu, W.; Li, Z.P.; Yu, G.C.; Ding, X.R.; Wang, J.Z.; Bo, X.C.; Zheng, X.F.; Zhou, Z.; Wang, S.Q., Cellular microRNA let-7c inhibits M1 protein expression of the H1N1 influenza A virus in infected human lung epithelial cells. *J Cell Mol Med,* **2012**, *16*, (10), 2539-2546.
[78] Yin, H.; Fan, Z.; Li, X.; Wang, J.; Liu, W.; Wu, B.; Ying, Z.; Liu, L.; Liu, Z.; Li, J., Phylogenetic tree-informed microRNAome analysis uncovers conserved and lineage-specific miRNAs in Camellia during floral organ development. *Journal of experimental*

botany, **2016**, *67*, (9), 2641-2653.
[79] Tarver, J.E.; Sperling, E.A.; Nailor, A.; Heimberg, A.M.; Robinson, J.M.; King, B.L.; Pisani, D.; Donoghue, P.C.; Peterson, K.J., miRNAs: small genes with big potential in metazoan phylogenetics. *Molecular biology and evolution,* **2013**, *30*, (11), 2369-2382.
[80] Patel, V.D.; Capra, J.A., Ancient human miRNAs are more likely to have broad functions and disease associations than young miRNAs. *BMC genomics,* **2017**, *18*, (1), 672.
[81] Wang, H., A protocol for investigating the association of vaccination and anti-NMDA receptor encephalitis. *Front Biosci (Schol Ed),* **2018**, *10*, (10), 229-237.
[82] Wang, H., The distance distribution of human microRNAs in MirGeneDB database. *Sci Rep,* **2022**, *12*, (1), 17696.
[83] Wang, H.; Ho, C., The Human Pre-miRNA Distance Distribution for Exploring Disease Association. *International Journal of Molecular Sciences,* **2023**, *24(2)*, 1009.
[84] Eliasson, L., The small RNA miR-375 - a pancreatic islet abundant miRNA with multiple roles in endocrine beta cell function. *Mol Cell Endocrinol,* **2017**, *456*, 95-101.
[85] Poy, M.N.; Hausser, J.; Trajkovski, M.; Braun, M.; Collins, S.; Rorsman, P.; Zavolan, M.; Stoffel, M., miR-375 maintains normal pancreatic alpha- and beta-cell mass. *Proc Natl Acad Sci U S A,* **2009**, *106*, (14), 5813-5818.
[86] Wang, H., MicroRNA, Diabetes Mellitus and Colorectal Cancer. *Biomedicines,* **2020**, *8*, (12).
[87] Keller, D.M.; Perez, I.G., Dual regulation of miR-375 and CREM genes in pancreatic beta cells. *Islets,* **2022**, *14*, (1), 139-148.
[88] Pashangzadeh, S.; Motallebnezhad, M.; Vafashoar, F.; Khalvandi, A.; Mojtabavi, N., Implications the Role of miR-155 in the Pathogenesis of Autoimmune Diseases. *Front Immunol,* **2021**, *12*, 669382.
[89] Kalkusova, K.; Taborska, P.; Stakheev, D.; Smrz, D., The Role of miR-155 in Antitumor Immunity. *Cancers (Basel),* **2022**, *14*, (21).
[90] Jafarzadeh, A.; Naseri, A.; Shojaie, L.; Nemati, M.; Jafarzadeh, S.; Bannazadeh Baghi, H.; Hamblin, M.R.; Akhlagh, S.A.; Mirzaei, H., MicroRNA-155 and antiviral immune responses. *Int Immunopharmacol,* **2021**, *101*, (Pt A), 108188.
[91] Kamolratanakul, S.; Pitisuttithum, P., Human Papillomavirus Vaccine Efficacy and Effectiveness against Cancer. *Vaccines (Basel),* **2021**, *9*, (12).
[92] Chung, J.Y.; Lee, S.J.; Shin, B.S.; Kang, H.G., Myasthenia gravis following human papillomavirus vaccination: a case report. *BMC Neurol,* **2018**, *18*, (1), 222.
[93] He, N.; Leng, X.; Zeng, X., Systemic lupus erythematosus following human papillomavirus vaccination: A case-based review. *Int J Rheum Dis,* **2022**, *25*, (10), 1208-1212.
[94] Li, W.; Jia, D.; Tong, L.; Lun, Z.; Li, H., Anti-N-methyl-D-aspartate receptor

encephalitis induced by bilateral ovarian teratomas with distinct histopathologic types: A case report and brief literature review. *Medicine (Baltimore),* **2019**, *98*, (48), e18148.
[95] Senkomago, V.; Henley, S.J.; Thomas, C.C.; Mix, J.M.; Markowitz, L.E.; Saraiya, M., Human Papillomavirus-Attributable Cancers - United States, 2012-2016. *MMWR Morb Mortal Wkly Rep,* **2019**, *68*, (33), 724-728.