Cellular and Molecular Neurobiology
https://doi.org/10.1007/s10571-021-01058-7

REVIEW PAPER

Single-Nucleotide Variants in microRNAs Sequences or in their Target Genes Might Influence the Risk of Epilepsy: A Review

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Received: 6 December 2020 / Accepted: 9 February 2021

Abstract

Single-nucleotide variant (SNV) is a single base mutation at a specific location in the genome and may play an import role in epilepsy pathophysiology. The aim of this study was to review case–control studies that have investigated the relationship between SNVs within microRNAs (miRs) sequences or in their target genes and epilepsy susceptibility from January 1, 2010 to October 31, 2020. Nine case–control studies were included in the present review. The mainly observed SNVs associated with drug-resistant epilepsy (DRE) risk were SNVs n.60G > C (rs2910164) and n.-411A > G (rs57095329), both located at miR-146a mature sequence and promoter region, respectively. In addition, the CC haplotype (rs987195-rs969885) and the AA genotype at rs4817027 in the MIR155HG/miR-155 tagSNV were also genetic susceptibility markers for early-onset epilepsy. MiR-146a has been observed as upregulated in human astrocytes in epileptogenesis and it regulates inflammatory process through NF-κB signaling by targeting tumor necrosis factor-associated factor 6 (*TRAF6*) gene. The SNVs rs2910164 and rs57095329 may modify the expression level of mature miR-146a and the risk for epilepsy and SNVs located at rs987195-rs969885 haplotype and at rs4817027 in the MIR155HG/miR-155 tagSNV could interfere in the miR-155 expression modulating inflammatory pathway genes involved in the development of early-onset epilepsy. In addition, SNVs rs662702, rs3208684, and rs35163679 at 3′untranslated region impairs the ability of miR-328, let-7b, and miR-200c binding affinity with paired box protein PAX-6 (*PAX6*), BCL2 like 1 (*BCL2L1*), and DNA methyltransferase 3 alpha (*DNMT3A*) target genes. The SNV rs57095329 might be correlated with DRE when a larger number of patients are evaluated. Thus, we concluded that the main drawback of most of studies is the small number of individuals enrolled, which lacks sample power.

Keywords Epilepsy · microRNAs (miRs) · Single-nucleotide variants (SNVs) · Susceptibility

Abbreviations

3′-UTR	3′untranslated region
AARS	Alanyl-tRNA synthetase
ALDH7A1	Aldehyde dehydrogenase 7 family member A1
ALG13	Asparagine-linked glycosylation 13
BCL2L1	BCL2 like 1
CI	Confidence interval
DNA	Deoxyribonucleic acid
DNMT3A	DNA methyltransferase 3 alpha
DRE	Drug-resistant epilepsy
NF-kB	Factor nuclear kappa B
GABA	Gamma-aminobutyric acid
IFN-Ɣ	Interferon-gamma
IL-1	Interleukin 1
IL-1β	Interleukin 1 beta
IRAK1	Interleukin 1 receptor associated kinase 1
ILAE	International league against epilepsy
MTLE	Mesial temporal lobe epilepsy
miRs	MicroRNAs
NMDA	N-Methyl-D-aspartate
OR	Odds ratio
OMIM	Online mendelian inheritance in man

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PAX-6	Paired box protein PAX-6
PCR	Polymerase chain reaction
RISC	RNA-induced silencing complex
RNA	Ribonucleic acid
SNVs	Single-nucleotide variants
SCN1A	Sodium voltage-gated channel alpha subunit 1
*SCN2*A	Sodium voltage-gated channel alpha subunit 2
SCN1B	Sodium voltage-gated channel beta Subunit 1
TlE	Temporal lobe epilepsy
TNF-α	Tumor necrosis factor alpha
*TRAF*6	Tumor necrosis factor receptor (TNFR)-associated actor 6
WHO	World Health Organization

Introduction

Epilepsy is a chronic brain disorder defined by at least two unprovoked seizures that occur within 24 h (Fisher et al. 2014). The disease affects about 50 million people worldwide at all ages (WHO 2019). The seizures are divided into focal, generalized, and unknown onset, according to the International league against epilepsy (ILAE) classification (Scheffer et al. 2017). The focal seizure is more common than generalized in children and adults (Beghi 2020), and the temporal lobe epilepsy (TLE) is the most common focal epilepsy subtype (Johnson 2019). In addition, TLE is the most common type of drug-resistant epilepsy (DRE) (Asadi-Pooya et al. 2017).

ILAE (Scheffer et al. 2017) has defined six etiologic categories for epilepsy as (a) structural etiology, a finding on neuroimaging reasonably inferred to cause the patient's seizures (Lapalme-Remis and Cascino 2016); (b) variant in a gene or copy number variant, which is pathogenic for epilepsy. The family history and typical features as electroencephalography and seizure semiology might be sufficient for genetic etiology (Hildebrand et al. 2013); (c) infectious etiology for patients with epilepsy due to the neurocysticercosis, human immunodeficiency virus, cytomegalovirus or cerebral toxoplasmosis (Vezzani et al. 2016); (d) metabolic epilepsies for patients with epilepsy due to a metabolic derangement such as pyridoxine-dependent seizures and cerebral folate deficiency (Parikh et al. 2015); (e) auto-immune diseases as encephalitis, which has been linked to both neuronal intracellular and neuronal cell surface antibodies (Toledrano and Pittock 2015); (f) unknown etiology for patients whose etiology remains unclear (Falco-Walter et al. 2018).

The genomic technology advances have greatly increased the knowledge on the epilepsy basis and genetic changes. Wang et al. (Wang et al. 2017) have evaluated the Online Mendelian Inheritance in Man (OMIM) database and the authors have found 84 epilepsy-related genes, being the sodium voltage-gated channel alpha subunit 1A (*SCN1A*) gene, the mainly observed one (Perucca and Perucca 2019). The most common epilepsy genes were ion-channel genes (*SCN1A, SCN1B, SCN2A*, others), totalizing 28 of the 84 epilepsy-related genes. Mutations in enzyme/enzyme-modulator genes as alanyl-tRNA synthetase (*AARS*), aldehyde dehydrogenase 7 family member A1 (*ALDH7A1*), and asparagine-linked glycosylation 13 (*ALG13*) ranked as the second cause (25/84 epilepsy-related genes). The remaining genes were involved in transport, receptor binding, cell adhesion, signal transduction/molecule, membrane trafficking, cytoskeleton, nucleic acid binding, and other unknown functions (Wang et al. 2017).

Recently, the role of microRNAS (miRs) in the epilepsy pathophysiology have been also described as biomarkers and novel therapy approaches for epilepsy (Ma 2018). Interestingly, single-nucleotide variants (SNVs) in miRs sequences or in their 3′untranslated region (3′-UTR) target genes might influence the risk for epilepsy and expression on their target genes, increasing diseases susceptibility, including epilepsy (Tao et al. 2015; Li et al. 2016b; Panjwani et al. 2016; Xiao et al. 2019; Boschiero et al. 2020). Thus, the aim of this study was to review case–control studies, which investigated the relationship between SNVs in miRs and in their target genes and risk for epilepsy.

The Biogenesis of miRs

The biogenesis of miR begins in the cell nucleus, from the transcription of DNA to pri-miR, by the action of the enzymes PASHA and DROSHA. The pri-miR undergoes action of the enzyme exportin-5 and it is exported to the cell cytoplasm where it gives rise to the pre-miR. This is catalyzed by another enzyme, Dicer, finally forming the mature miR. Mature miR is associated with a complex or set of enzymes called RNA-induced silencing complex (RISC) and suppresses or inhibits protein synthesis by cleavage of messenger RNAs (mRNAs) or by preventing translation of mRNAs, inhibiting protein production (Hata and Kashima 2016).

SNVs in miRs and Epilepsy

MiRs, discovery in 1980 (Horvitz and Sulston 1980) and subsequently existence confirmed in 2001 (Lee and Ambros 2001), ushered a new era in molecular biology. MiRs are short non-coding regulatory RNAs with 19 to 25 nucleotides (nt) in size, responsible for post-transcriptional silencing regulating of their target genes expression (Lu and Rothenberg 2018). Base-pairing occurs between the miR and

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target gene, often within the 3′-UTR of the mRNA, resulting in recruitment of additional factors that lead to either degradation of the mRNA or inhibition of translation (Krol et al. 2010; Meister 2013). In mammals, 60% of the mRNAs have a known seed sequence for miR-binding; thus, in the brain, miRs are particularly abundant and control neurogenesis (Kosik 2006). In Dicer knockout mouse model, the biogenesis of miR is blocked, leading to neuronal loss and premature animal death (Schaefer et al. 2007).

Noteworthy, the majority of the known miRs are expressed in the brain and many such as miR-124 has elevated expression in the brain cells, but less detectable in other tissues (Lagos-Quintana et al. 2002; Miska et al. 2004; Shao et al. 2010; Ludwig et al. 2016). Furthermore, excitatory and inhibitory neurons, astrocytes, microglia, and oligodendrocytes express specific miRs (He et al. 2012; Jovicic et al. 2013). In contrast, individual miRs loss can also be sufficient to produce central nervous system phenotypes as the loss of miR-9 that results in brain development defects (Shibata et al. 2011), the loss of miR-124, which results in hippocampus neurodegeneration (Sanuki et al. 2011), and the postnatal deletion of miR-128 from dopaminergic neurons results in epilepsy (Tan et al. 2013).

Recently, the role of miRs in the epilepsy pathophysiology have been described on synaptic structure and function (miR-134, miR-128, miR-203 and miR-139), neurogenesis and neuronal migration (miR-134, miR-128, miR-124 and miR-137), inflammation (miR-146 and miR-22), transcription (miR-132, miR-124 and miR-199), and cell death (miR-34a and miR-184) (Brennan and Henshall 2018).

The SNVs in miRs are examples of point mutations that could affect miR function in three possible ways: altering transcription of the primary miR transcript, processing primary miR (pri-miR) and precursor miR (pre-miR), and by their effects on the modulation of miR-mRNA interplay (Saunders et al. 2007; Duan et al. 2007). Subsequently, SNVs in miRs have been associated with several brain pathogenesis like Parkinson's disease, Alzheimer's disease, or other neurodegenerative diseases (Quinlan et al. 2017; Wang et al. 2017; Dehghani et al. 2018) and might also increase the risk for epilepsy (Manna et al. 2013). SNV is a substitution of a single nucleotide that occurs at a specific position in the genome and the most common source of genetic polymorphism in the human genome accounts about 90% of all polymorphisms (Dabhi and Mistry 2014).

In the present review, only six case–control studies have evaluated SNVs in miRs sequence and risk for epilepsy (Table 1). The most evaluated SNVs associated with epilepsy susceptibility were SNVs n.60G > C (rs2910164) and n.-411A > G (rs57095329), both located at miR-146a mature sequence and promoter region, respectively (Manna et al. 2013; Cui et al. 2015; Issac et al. 2015; Li et al. 2016b; Boschiero et al. 2020). In addition, the CC haplotype (rs987195-rs969885) and the AA genotype at rs4817027 in the MIR155HG/miR-155 tagSNV were also genetic susceptibility markers for early-onset epilepsy (Tao et al. 2015).

Neuroinflammatory signaling is partially controlled by miR-146a and overexpression of miR-146a following status epilepticus potently suppresses recurrent seizures in mice models (Iori et al. 2017). In addition, miR-146a has been observed to be upregulated in human epileptic astrocytes (Lukiw et al. 2008) and it regulates inflammatory process through the nuclear factor kappa B (NF-κB) signaling by targeting tumor necrosis factor-associated factor 6 (*TRAF6*) gene (Taganov et al. 2006; Hou et al. 2009). The SNVs rs2910164 and rs57095329 in the miR-146a may alter the expression level of the mature miR-146a (Zhou et al. 2014; Boschiero et al. 2020) and the risk of epilepsy.

Only four studies have evaluated the association of epilepsy risk and the SNV rs2910164 in the pre-miR-146a (Manna et al. 2013; Cui et al. 2015; Issac et al. 2015; Boschiero et al. 2020). (Manna et al. 2013) tested the rs2910164 and susceptibility to TLE in an Italian population cohort and analysis comparing genotypes and alleles' frequencies in patients and controls showed no significant differences, including clinical characteristics. (Cui et al. 2015) evaluated the SNV rs2910164 in Chinese TLE and non-TLE patients and the authors found that the SNV rs2910164 was not associated with epilepsy in both groups. (Issac et al. 2015) has examine whether SNV rs2910164 effected the proinflammatory cytokine, serum high-mobility group box 1 levels, in Egyptian children presenting febrile seizures. The authors discovered that rs2910164 polymorphism was not associated with elevated risk of febrile seizures. However, higher high-mobility group box 1 levels in rs2910164 CC compared to GG genotype was observed. Finally, (Boschiero et al. 2020) have observed an increased frequency of rs2910164 GC in brain tissues from DRE patients with two times risk for epilepsy. The Brazilian population is extremely mixed (dos Santos et al. 2013), which may explain the contrasting results. Thus, the discrepancy among the studies might be due to ethnic variation and differences in number of recruited patients.

Only three groups (Cui et al. 2015; Li et al. 2016b; Boschiero et al. 2020) have studied the SNV rs57095329 in patients with epilepsy. The study of (Cui et al. 2015) described that the rs57095329 A allele was associated with a reduced risk of seizures frequency in Chinese DRE patients. In contrast, (Li et al. 2016b) observed in Chinese childhood epilepsy patients that the G allele of rs57095329 could increase drug-resistance risk and seizure severity, but no genotype risk association was observed by authors. (Boschiero et al. 2020) have included only DRE patients and, most of the patients and controls were equally heterozygous for

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Table 1 Association between single-nucleotide variants (SNVs) within microRNAs (miRs) sequences and epilepsy

References	Population	Associated disease	SNV	miRs	miRs-target genes	Genotypes Risk	Putative risk alleles	OR (95%CI)
Boschiero et al. (2020)	Brazil	Control vs. TLE/DRE	rs2910164 G > C	*miR-146a*	*NF-kB*	**GG/GC (p = 0.04)**		1.98 (1.19–3.57)
						GG/CC ($p = 0.06$)		1.18 (0.27–3.97)
						GC/GG + CC (p = 0.023)		**1.90 (1.10–3.9)**
						GG/GC + CC (p = 0.047)		0.54 (0.30–0.96)
						CC/GG + GC ($p = 1.00$)		0.81 (0.20–2.52)
							C/G ($p = 0.283$)	1.98 (1.19–3.57)
			rs57095329 A > G			AA/GA + GG ($p = 0.597$)		–
						GA + GG/AA ($p = 0.587$)		–
						AA + AG/GG ($p = 0.703$)		1.46 (0.24–6.33)
						AA + GG/GA ($p = 0.703$)		1.73 (0.38–16.24)
							A/G ($p = 0.721$)	1.08 (0.72–1.60)
Manna et al. (2016)	Italy	Control vs. MTLE	rs531564 C > G	*miR-124*	*Neuronal differentiation*	CC/CG/GG ($p = 0.579$)	C/G ($p = 0.293$)	1.21 (0.85–1.71)
Li et al. (2016b)	China	Control vs. epilepsy	rs57095329 A > G	*miR-146a*	*NF-kB*	AA/GA ($p = 0.945$)	–	1.01 (0.69–1.49)
						AA/GG ($p = 0.089$)	–	1.27 (0.97–1.66)
						AA/GA + GG ($p = 0.405$)	–	1.16 (0.8–1.64)
						AA + GA/GG ($p = 0.087$)	–	1.58 (0.94–2.69)
			rs2292832 T > C	*miR-149*	*TNF-α NF-kB*	TT/TC ($p = 0.914$)		0.98 (0.68–1.41)
						TT/CC ($p = 0.433$)		1.12 (0.85–1.48)
						TT/TC + CC ($p = 0.837$)		1.04 (0.74–1.46)
						TT + TC/CC ($p = 0.356$)		1.28 (0.76–2.16)

Table 1 (continued)

References	Population	Associated disease	SNV	miRs	miRs-target genes	Genotypes Risk	Putative risk alleles	OR (95%CI)
			rs11614913 T > C	*miR-196a2*	*TNF-α NF-kB*	TT/TC ($p = 0.986$)		1.00 (0.67–1.52)
						TT/CC ($p = 0.696$)		1.05 (0.82–1.34)
						TT/TC + CC ($p = 0.895$)		1.03 (0.70–1.51)
						TT + TC/CC ($p = 0.566$)		1.13 (0.75–1.69)
			rs3746444 A > G	*miR-499*	*TNF-α NF-kB*	AA/GA ($p = 0.917$)		1.02 (0.69–1.51)
						AA/GG ($p = 0.438$)		0.88 (0.63–1.22)
						AA/GA + GG ($p = 0.817$)		0.96 (0.67–1.37)
						AA + GA/GG ($p = 0.422$)		0.77 (0.40–1.46)
		DRE vs. drug responsive	rs57095329 A > G	*miR-146a*	*NF-kB*	**AA/GA (p = 0.005)**		**2.34 (1.30–4.21)**
						AA/GG (p = 0.002)		**1.79 (1.24–2.59)**
						AA/GA + GG (p < 0.001)		**2.63 (1.56–4.43)**
						AA + GA/GG (p = 0.017)		**2.34 (1.17–4.67)**
							G (p < 0.001)	**2.36 (1.61–3.47)**
			rs2292832 T > C	*miR-149*	*TNF-α NF-kB*	TT/TC ($p = 0.849$)	–	0.95 (0.55–0.64)
						TT/CC ($p = 0.962$)		0.99 (0.67–1.47)
						TT/TC + CC ($p = 0.849$)		1.05 (0.63–1.75)
						TT + TC/CC ($p = 0.969$)		1.02 (0.49–2.11)
			rs11614913 T > C	*miR-196a2*	*TNF-α NF-kB*	TT/CT ($p = 0.992$)	–	0.99 (0.54–1.86)
						TT/CC ($p = 0.894$)		0.99 (0.67–1.47)
						TT/TC + CC ($p = 0.902$)		1.05 (0.63–1.75)

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Table 1 (continued)

References	Population	Associated disease	SNV	miRs	miRs-target genes	Genotypes Risk	Putative risk alleles	OR (95%CI)
						TT + TC/CC ($p = 0.775$)		1.02(0.49–2.11)
			rs3746444 A > G	*miR-499*	*TNF-α NF-kB*	AA/GA ($p = 0.837$)	–	1.06 (0.60–1.88)
						AA/GG ($p = 0.595$)	–	0.86 (0.499–1.49)
						AA/GA + GG ($p = 0.968$)	–	1.01 (0.592–1.73)
						AA + GA/GG ($p = 0.529$)	–	1.41 (0.48–4.13)
Cui et al. (2015)	China	Control vs. total cases	rs2910164 G > C	*miR-146a*	*NF-kB*	CC/CG/GG ($p = 0.150$)	C/G ($p = 0.328$)	1.15 (0.89–1.48)
		Control vs. TLE				CC/CG/GG ($p = 0.265$)	C/G ($p = 0.567$)	1.09 (0.825–1.45)
		Control vs. no-TLE				CC/CG/GG ($p = 0.282$)	C/G ($p = 0.214$)	1.28 (0.87–1.88)
		Control vs. total cases	rs57095329 A > G	*miR-146a*	*NF-kB*	AA/GA/GG ($p = 0.754$)	C/G ($p = 0.523$)	1.12 (0.82–1.54)
		Control vs. TLE				AA/GA/GG ($p = 0.968$)	C/G ($p = 0.862$)	1.04 (0.74–1.47)
		Control vs. no-TLE				AA/GA/GG ($p = 0.410$)	C/G ($p = 0.241$)	1.35 (0.83–2.20)
		Control vs. DRE	rs2910164 G > C	*miR-146a*	*NF-kB*	CC/CG/GG($p = 0.650$)	C/G ($p = 0.506$)	1.14 (0.78–1.66)
		Control vs. DRE	rs57095329 A > G	*miR-146a*	*NF-kB*	**AA/GA/GG ($p = 0.026$)**	G ($p = 0.011$)	–
Tao et al. (2015)	China	Control vs. DRE	rs969885 C > T	*miR-155*	*Inflammatory pathways*	CC/CT/TT ($p = 0.536$)	C/T ($p = 0.548$)	0.79 (0.36–1.72)
						CC/CT + TT ($p = 0.717$)		0.85 (0.36–2.04)
						CC + CT/TT ($p = 0.233$)		**5.07 (0.35–73.13)**
			rs12483428 T > C	*miR-155*	*Inflammatory pathways*	TT/TC/CC ($p = 0.516$)	T/C ($p = 0.511$)	1.27 (0.63–2.57)
						TT/TC + CC ($p = 0.542$)		1.29 (0.57–2.90)
						TT + TC/CC ($p = 0.705$)		1.55 (0.16–14.83)

Table 1 (continued)

References	Population	Associated disease	SNV	miRs	miRs-target genes	Genotypes Risk	Putative risk alleles	OR (95%CI)
			rs987195 C > G	*miR-155*	*Inflammatory pathways*	CC/CG/GG ($p = 0.118$)	C/G ($p = 0.097$)	1.59 (0.92–2.75)
						CC/CG + GG ($p = 0.081$)		1.98 (1.92–4.28)
						CC + CG/GG ($p = 0.448$)		1.48 (0.54–4.03)
			rs4817027 G > A	*miR-155*	*NF-kB*	GG/GA/AA ($p = 0.074$)	G/A ($p = 0.094$)	1.72 (0.91–3.24)
						GG/GA + AA ($p = 0.213$)		1.63 (0.76–3.52)
						GG + GA/AA ($p = 0.024$)		**13.13 (1.40–123.83)**
Manna et al. (2013)	Italy	Control vs. TLE	rs2910164 G > C	*miR-146a*	*NF-kB*	GG/GC/CC ($p = 0.536$)	G/C ($p = 0.361$)	1.10 (0.89–1.36)
						GG/CG		1.17 (0.88–1.55)
						GG/CC		1.10 (0.65–1.8)

SNVs single-nucleotide variants, *miRs* microRNAS, *vs.* versus, *OR* odds ratio with 95% confidence intervals, *TLE* temporal lobe epilepsy, *DRE* drug-resistant epilepsy, *MTLE* mesial temporal lobe epilepsy, *TNF-α* tumor necrosis factor alpha, *NF-KB* factor nuclear Kappa B

the SNV rs57095329 with no genotype risk association. Epilepsy is a multifactorial disorder in which genetic susceptibility and environmental factors may be implicated; larger patients cohort are needed to confirm the possible clinical association of rs57095329.

Recently, it was investigated the association of SNVs rs2292832, rs11614913, and rs3746444 in the precursor sequences of miR-149, miR-196a2, and miR-499, respectively in neurodegenerative disorder as Parkinson (Haixia et al. 2012). Interestingly, the three miRs also modulate genes related to inflammation pathways including tumor necrosis factor-α (TNF-α), toll-like receptor signaling, and cytokine response (Haixia et al. 2012). Li et al. (2016b) have hypothesized that the SNVs rs2292832, rs11614913, and rs3746444 located at miRs precursor sequences may also contribute to childhood epilepsy risk. Thus, the authors have genotyped the three SNVs in a hospital-based case–control studies in a Chinese population and no interrelation with epilepsy risk was observed.

Furthermore, the effect of the SNV g.9903189C/G (rs531564) located at primary miR-124 on susceptibility to mesial temporal lobe epilepsy (MTLE), most common refractory epilepsy form, was investigated using a case control study in Italian population (Manna et al. 2016). The neuron-specific miR-124 have been showed to be essential for neuronal differentiation (Makeyev et al. 2007). Recently, miR-124 has been found to be upregulated in the acute and chronic seizure stages of MTLE (Peng et al. 2013). Therefore, (Manna et al. 2016) have determined whether SNV rs531564 could influence risk to MTLE patients. No statistically significant differences were found in the allele or genotype distributions of the miR-124 rs531564 polymorphism in patients and control groups evaluated.

Above studies were the first and unique to evaluate SNVs rs2292832, rs11614913, and rs3746444 in Chinese with epilepsy and the SNV rs531564 in Italian MTLE susceptibility, respectively. The findings need to be reproduced in a larger patients' cohort and other populations.

Both miR-146a and miR-155 are the most involved in the inflammatory process of epilepsy. Recently, a positive association between SNV rs2910464 in the miR-146a and Brazilian patients with DRE was evaluated by our team (Boschiero et al. 2020). The first report that MIR155HG/miR-155 tag SNVs are related to DRE was provided by Tao and collaborators (Tao et al. 2015). MiR-155 is a transcription product of its host gene, *MIR155HG*, and its expression could be affected by polymorphisms located at both *MIR155HG* and miR-155 genes in multiple sclerosis (Paraboschi et al., 2011). Thus, (Tao et al. 2015) have evaluated Chinese Han DRE patients and healthy individuals for the 4 tag SNVs rs969885, rs12483428, rs987195, and rs4817027, located at *MIR155HG/miR-155*. Their study has showed that the CC haplotype (rs987195-rs969885) is a genetic susceptibility

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marker for early-onset epilepsy. In addition, the authors have found that the AA genotype (rs4817027) and the CC haplotype (rs987195-rs969885) were genetic susceptibility markers for DRE. On the contrary, the CG haplotype (rs987195-rs969885) was a genetic protective factor against DRE. The results are compatible with the inflammatory mechanism of DRE.

In conclusion, most of the studies presented here were unique and the findings need to be reproduced in a larger patients' cohort in different populations. In addition, the GC and CC genotypes for SNV rs2910164 in miR-146a, the CC haplotype (rs987195-rs969885) and the AA genotype at rs4817027 for MIR155HG/miR-155 tag SNV, were genetic susceptibility markers for DRE or early-onset epilepsy, confirming the role of both miR-146a and miR-155 with inflammation response in the pathogenesis of epilepsy. MiR-146a is a NF-κB trans-activational target and negatively regulates interleukin 1 receptor associated kinase 1 (*IRAK1)* and *TRAF6*, being identified as a powerful innate immune and pro-inflammation regulator (Jazdzewski et al. 2008). The expression of *miR-155*, an inflammatory modulator, is significantly increased in the brain in an immature rat model of status epilepticus and in children with MTLE (Ashhab et al. 2013), suggesting that the inflammatory role of miR-155 is involved in the development of early-onset epilepsy.

In fact, an increasing amount of evidence has supported the hypothesis that inflammatory processes within the epileptic brain might constitute a common and crucial mechanism in the pathology of seizures (Vezzani 2014). Brain injury leads to the activation of the microglial cells, which increases the release of proinflammatory cytokines as interleukin (IL)-1, interferon-gamma (IFN-γ), and TNF-α, which further activate the NF- kB mediated pathway. At the same time, there is also a damage to the gamma-aminobutyric acid (GABA) GABAergic neurons in the brain, which leads to a relative increase in the excitatory transmitter like glutamate. Increased activation of the glutamate receptor lead to increase in the oxidative stress that ultimately activates the NF- kB through proinflammatory pathway (Singh et al. 2018). As a consequence of this action, N-methyl-D-aspartate (NMDA) receptor-mediated Ca^{2+} influx into neurons is enhanced by IL-1, and this effect plays a role in promoting excitotoxicity and seizure generation (Viviani et al. 2003; Balosso et al. 2008). Lubin and collaborators (Lubin et al. 2007) have found that inhibition of NF-kB significantly decreased seizure threshold in treated rats suggesting that NF-kB activation is neuroprotective following a variety of brain insults and neurodegenerative conditions, supporting the proposal that proinflammatory cytokines and the NF-κB pathway have a role in the pathogenesis of status epilepticus development (Zhang et al. 2018).

As previously commented, SNVs in miRs related to epilepsy might affect the levels of proteins associated with the disorder. However, most of the studies did not involve additional experiments to assess the miRs and its predicted targets expression, once obtaining tissue samples of epileptogenic foci is difficult. Thus, only (Boschiero et al. 2020) have evaluated the miR-146a expression level in the epileptogenic tissues, considering the different genotypes for the SNV rs2910164. The authors have observed lower miR-146a expression in the GC and CC genotypes compared to GG genotype. Also, *TRAF6* gene expression level was higher in GC and CC than in GG genotype.

SNVs in miRs Target Genes

The miR: mRNA pairing consequence is a protein expression loss, resulting from either decreased transcript levels or translational repression (Winter et al. 2009). Many mRNAs contain conserved miR target sites in their 3′-UTR. The average size of human highly expressed neuronal genes is 1300 nt, whereas for genes specific to non-neuronal tissue it is 700 nt (Lewis et al. 2005; Sood et al. 2006), while the efficient miR-binding site consists of 6–8 nt. The composition of specific miRs associated with the 3′-UTR of a mRNA along with the efficiency of miR pairing to their target sequences impacts the mRNA's half-life and influences protein levels (Filipowicz et al. 2008; Bartel 2009) Considering the complexity of miRNA: mRNA pairing, the introduction of a SNV into a 3′-UTR can introducing or removing miR target sequences or changing the binding efficiency. In addition, the introduction or removal of miR target sites may affect binding to other miR target sequences in the SNV's close proximity, which could have unpredicted effects on the mRNA half-life.

There are only 3 studies that have observed SNVs in the 3′-UTR of miRs target genes in epilepsy (Table 2). One study has observed that the SNV rs662702 of miRNA-328 binding site in the 3′-UTR of paired box protein PAX-6 (*PAX6*), which is known to result in increased *PAX6* expression, conferred the increased risk of centrotemporal spikes of Rolandic epilepsy (Panjwani et al. 2016).

Also, Li et al. (2016a) have investigated if genetic variants in 3′-UTR of *SCN1A*, affecting the miR-mRNA 3′-UTR interaction and *SCN1A* gene repression, potentially associated with epilepsy. The authors identified twelve variants, NM_001202435.1:n.6277A > G, n.6568_6571del, n.6761C > T, n.6874A > T, n.6907 T > C, n.6978A > G, n.7065_7066insG, n.7282 T > C, n.7338_7344del, n.7385 T > A, n.7996 C > T, and n.8212C > T in 3′-UTR of *SCN1A* gene. The authors have observed that the genotype distribution of n.7282 T > C was significantly different in the male group, being the homozygous variant (CC) and

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heterozygous (CT) much less frequent in male patients than in male controls (Table 2). Other two variants, n.7996C > T and n.8212C > T did not significantly distribute genotypes differently between cases and controls. In female subset, three variants were distributed relatively even in the patient and control group, n.7282 T > C, n.7996 C > T, and n.8212 C > T (Table 2). The genetic variant n.6978 A > G was fully deviated (variant GG, 100%) from that of the homozygous genotype (AA). The homozygous variants genotypes frequencies of n.6277 A > G, n.6568_6571del, n.6761 C > T, n.6874 A > T, n.6907 T > C, n.7065_7066insG, n.7338_7344del, and n.7385 T > A were quite low, one or two cases in some gender group (male group or female group).

More recently, (Xiao et al. 2019) have experimentally confirmed that SNV rs3208684 A > C in 3′-UTR of BCL2 like 1 (*BCL2L1*) impairs the ability of let-7b binding affinity with *BCL2L1*. Previous study have demonstrated that *BCL2L1*, an anti-apoptotic member of the Bcl-2 family, it was found to be overexpressed in human TLE, conferring a survival property to neural cells (Henshall et al. 2000). In addition, it was reported that let-7b could act as a key regulator in the intrinsic apoptotic pathway by targeting *BCL2L1* (Yan et al. 2017), since it was also verified previously that Let-7b is downregulated in TLE (McKiernan et al. 2012).

Using Luciferase report assays, Xiao and colleagues (Xiao et al. 2019) have demonstrated that miR-200c targeted 3′-UTR of the DNA methyltransferase 3 alpha (*DNMT3A*) gene expression and the SNV rs35163679, within the miR-200c binding site, influenced the ability of miR-200c binding affinity with *DNMT3A*. Previously, it was reported increased *DNMT3A* expression in patients with intractable TLE (Zhu et al. 2012). *DNMT3A* is a member of the DNA methyltransferase enzyme family, which promotes de novo methylation during development and regulate synaptic function in mature central nervous system neurons (Feng et al. 2010).

In conclusion, SNVs in the 3′-UTR of miRs target genes may be potential molecular pathological mechanisms of TLE and therapeutic targets; however, case–control studies including different ethnic populations need to be performed to confirm the results.

The SNV n.-411A > G (rs57095329) in *miR-146a* as a Risk Factor for DRE

As pointed out before, most of the studies were unique and the findings need to be reproduced in a larger patients' cohort in different populations. However, after a literature review, three similar studies for SNV rs57095329 at miR-146a was identified in DRE patients (Cui et al. 2015; Li et al. 2016b; Boschiero et al. 2020). In this context, we input all data for the SNV rs57095329 in a dataset, aiming first to compare the results and then, to have a better design to identify an association between SNV rs57095329 and DRE. Thus, we performed one subgroup data including all Chinese and Brazilian DRE patients versus healthy Chinese and Brazilian individuals.

The comparative association of the SNV rs57095329 in patients with DRE and controls groups are showed in Table 3. The percentage of different genotypes individually for the evaluated SNV was similar in the two Chinese studies; however, it was different for Brazilian patients (Boschiero et al. 2020).

Interestingly, after the association between Chinese and Brazilian samples, it was observed significantly genotype differences between patient and control groups. Thus, increased frequency of AA genotype was observed in patients compared to controls [55.98% versus (vs.) 41.60%, $p\text{-value} \leq 0.01$] with 1.78 [95% confidential interval (CI) = 1.43–2.22] risk for DRE (Table 3). The A allele presented significantly risk for the disease compared to G allele (68.37% vs. 61.34%, $p\text{-value} \leq 0.01$) with an Odds ratio (OD) of 1.36 (95%CI = 1.13–1.65).

Our results highlighted that the SNV rs57095329 might be correlated with DRE when a larger number of patients are evaluated. Thus, we concluded that the main drawback of most of studies is the small number of individuals enrolled, which lacks sample power. Epilepsy is a multifactorial disorder in which genetic susceptibility and environmental factors may be implicated; larger cohort from different countries including patients with DRE and patients' drug-responsiveness are needed to confirm the possible association of SNV rs57095329.

Conclusions

- The most evaluated SNVs associated with DRE risk were SNVs n.60G > C (rs2910164) and n.-411A > G (rs57095329), both located at miR-146a mature sequence and promoter region, respectively.
- MiR-146a has been identified to be involved in the upregulation of inflammatory responses in human astrocytes in epileptogenesis through NF-κB signaling by targeting *TRAF6* gene and miR-155 has been reported as inflammatory pathway genes modulator in early-onset epilepsy development.
- The CC haplotype (rs987195-rs969885) and the AA genotype at rs4817027 in the MIR155HG/miR-155 tag SNV were associated with early-onset epilepsy.
- SNVs rs662702, rs3208684, and rs35163679 at 3′-UTR impairs the ability of miR-328, let-7b, and miR-200c binding affinity with *PAX6*, *BCL2L1*, and *DNMT3A* target genes, indicating that SNVs in 3′-UTR of target genes may be potential molecular pathological mechanisms of

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Table 2 Association between single-nucleotide variants (SNVs) in the 3′untranslated region (UTR) of microRNAs (miRs) target genes and epilepsy

References	Population	Methods	SNVs	3′-UTR genes	miRs	Putative risk alleles	**OR (95%IC)**
Panjwani et al. (2016)	US, Canada, Argentina, France and the UK	Control vs. Rolandic epilepsy	rs662702 C > T	*PAX6*	*miR-328*	**CC/CT/TT ($p = 2.6 \times 10^{-4}$)**	**12.29 (3.20–7.22)**
Li et al. (2016a)	China	Control vs. epileptic patients	n.6277A > G	*SCN1A*	–	–	–
			n.6568_6571del	*SCN1A*	–	–	–
			n.6761C > T	*SCN1A*	–	–	–
			n.6874A > T	*SCN1A*	–	–	–
			n.6907 T > C	*SCN1A*	–	–	–
			n.6978A > G	*SCN1A*	–	–	–
			n.7065_7066insG	*SCN1A*	–	–	–
			n.7282 T > C	*SCN1A*	–	**TT/CC + CT ($p < 0.05$) (Male patient)** TT/CT/TT ($p > 0.05$) (*Female patient*)	0.42 (1.61–0.11) 1.50 (0.36–1.17)
			n.7338_7344del	*SCN1A*	–	–	–
			n.7385 T > A	*SCN1A*	–	–	–
			n.7996 C > T	*SCN1A*	–	CC + CT/TT ($p > 0.05$) CC/CT/TT ($p > 0.05$) (*Female patient*)	0.875 (0.89–0.62) 0.91 (0.86–0.68)
			n.8212C > T	*SCN1A*	–	CC/CT + TT ($p > 0.05$) CC/CT/TT ($p > 0.05$) (Female *patient*)	0.77 (1.12–0.60) 1.03 (0.94–1.01)
Xiao et al. (2019)	–	Luciferase report assay	rs3208684 A > C	*BCL2L1*	*let-7b*	–	–
		Luciferase report assay	rs35163679	*DNMT3A*	*miR-200c*	–	–

SNVs single-nucleotide variants, *3´-UTR* 3′untranslated region, *vs.* versus, *OR* odds ratio with 95% confidence intervals, *US* United States of America, *UK* United Kingdom, *miRs* microRNAS, *DNMT3A* DNA methyltransferase 3 alpha, *PAX6* paired box protein PAX-6, *BCL2L1* BCL2 like 1, *SCN1A* sodium voltage-gated channel alpha subunit 1

TLE; however, case–control studies including different ethnic populations need to be performed.

- SNV rs57095329 might be correlated with DRE when a larger number of patients are evaluated. Thus, we concluded that the main drawback of most of studies is the small number of individuals enrolled, which lacks sample power.

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Table 3 Comparative association of the single-nucleotide variant n.-411A > G (rs57095329) in *miR-146A* in patients with drug-resistant epilepsy and health control groups

Genotypes	Patients n (%) A	Controls n (%) A	Odds ratio (95%CI)		
			Additive (AA vs. GA vs. GG)	Dominant (GA + GG vs. AA)	Recessive (AA + GA vs. GG)
AA	0 (0.00)	5 (2.14)	NA	NA	Reference
GA	58 (95.08)	221 (94.44)	NA	NA	Reference
GG	3 (4.92)	8 (3.42)	NA	NA	1.46 (0.242–6.33)
p-value by model			0.597*	0.587*	0.703*
Genotypes	Patients n (%) B	Controls n (%) B	Additive	Dominant	Recessive
AA	160 (59.93)	152 (56.93)	NA	1.13 (0.80–1.60)	Reference
GA	89 (33.33)	76 (28.46)	NA	Reference	Reference
GG	18 (6.74)[a]	39 (14.61)	NA	Reference	0.42 (0.24–0.76)
p-value by model			≤0.01**	0.482** (0.405#)	0.003** (0.087#)
Genotypes	Patients n (%) C	Controls n (%) C	Additive	Dominant	Recessive
AA	163 (65.46)	155 (62.25)	NA	1.15 (0.80–1.66)	Reference
GA	79 (31.73)	86 (34.54)	NA	Reference	Reference
GG	7 (2.81)	8 (3.21)	NA	Reference	0.87 (0.31–2.44)
p-value by model			0.754**	0.456**	0.793**
Genotypes	Patients n (%)—Total	Controls n (%)—Total	Additive	Dominant	Recessive
AA	323 (55.98)[b]	312 (41.60)	NA	1.79 (1.43–2.22)	Reference
GA	226 (39.17)	383 (51.07)	NA	Reference	Reference
GG	28 (4.85)	55 (7.33)	NA	Reference	0.65 (0.40–1.03)
p-value by model			≤0.01**	≤0.01**	0.068**
Allele	Patients n (%)—Total		Controls n (%)—Total		Allelic analysis
A	323 (68.37)		695 (61.34)		1.36 (1.13–1.65)
G	254 (31.63)		438 (38.66)		Reference
p-value					≤0.01**

*Fisher's test

**Chi-square

#Adjusted odds ratio based on age and sex. *OR* odds ratio, *95%CI* 95% confidence interval, *NA* not applicable

[A]Boschiero et al. 2020

[B]Li et al. 2016a, b

[C]Cui et al. 2015

Author contributions Conception and design: MMO; acquisition of data: RPB, MNB, BC; analyses and interpretation of data: MMO, FALM, PHPA; statistical analyses: FALM; drafting of the manuscript: RPB, MMO; study supervision: MMO. All authors were involved in revision of the manuscript and have approved the final version.

Funding The financial support provided for this work by the São Paulo Research Foundation (FAPESP) scholarship# 2018/12057-0, and National Council for Scientific and Technological Development (CNPq) scholarship#149884/2019-2, are gratefully acknowledged.

Data Availability The data and material will be available on request.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics Approval This study was approved by the Ethic Committee of Universidade São Francisco (USF) (CAAE: 90786718.1.0000.5514). We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Consent for Publication All the authors gave the consent for publication.

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Journal : **Large 10571**	Article No : **1058**	Pages : **14**	MS Code : **1058**	Dispatch : **26-2-2021**