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RESEARCH ARTICLE

The Computational Analysis Conducted on miRNA Target Sites in Association with SNPs at 3'UTR of ADHD-implicated Genes

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Abstract: ***Background*:** Attention-deficit/hyperactivity disorder (ADHD) is a frequent chronic neuropsychiatric disorder in which different factors including environmental, genetic, and epigenetic factors play an important role in its pathogenesis. One of the effective epigenetic factors is recognized as MicroRNAs (miRNAs). On the other hand, it has been indicated that the single nucleotide polymorphism (SNPs) present within 3'UTR (3' untranslated region) of mRNAs can influence the regulation of miRNA-mediated gene and susceptibility to a diversity of human diseases.

***Methods*:** The purpose of this study was to analyze the SNPs within the 3'UTR of miRNA target genes associated with ADHD. 3'UTR genetic variants were identified in all genes associated with ADHD using DisGeNET, dbGaP, Ovid, DAVID, Web of knowledge, and SNPs databases. miRNA's target prediction databases were applied in order to predict the miRNA binding sites. 124 SNPs with MAF>0.05 were identified located in the binding site of the miRNA of 35 genes amongst 51 genes associated with ADHD.

***Results*:** Bioinformatics analysis predicted 81 MRE (miRNA recognition elements)-creating SNPs, 101 MRE-breaking SNPs, 61 MRE-enhancing SNPs, and finally predicted 41 MRE-decreasing SNPs in the 3'UTR of ADHD-implicated genes. These candidate SNPs within these genes miRNA binding sites can alter the miRNAs binding, and consequently, lead to mRNA gene regulation.

***Conclusion*:** Therefore, these miRNA and MRE-SNPs may play important roles in ADHD, and because of that, they would be valuable for further investigation in the field of functional verification.

Keywords: ADHA, SNP, miRNA, miRNA binding sites, ADHD- related genes, miRNA target genes.

1. INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is known as a neurodevelopmental disorder [1]. It is characterized by different inattention, hyperactivity, and impulsivity levels [2]. This disorder prevalence has been estimated as 2.5 -4.9% in adults and 5% in children [3]. ADHD is identified as a multifactorial disorder, and all three environmental, genetic, and epigenetic factors play significant roles in this disorder pathogenesis [4]. One of these epigenetic factors is MicroRNAs (miRNAs). Much research has indicated that alterations in the miRNAs expression or function are associated with ADHD, schizophrenia, autism, bipolar disorder, and other intellectual disorders [5]. miRNAs are considered as important non-coding RNAs class with 18-25 nucleotide length, which regulates gene expression post-transcriptionally. miRNAs are involved in different biological processes including neuronal cell growth, specification, development, differentiation, synaptic plasticity, and also memory formation [6]. The miRNAs critical region is the "seed" region (2-7 nt from 5' end of miRNAs), which in the 3'UTR (3' untranslated region) of the mRNA preferentially binds to a target site named as miRNA recognition elements (MREs) [7].

Therefore, any disturbance in miRNA-MRE interactions could have an influence on gene expression regulation. Single Nucleotide Polymorphisms (SNPs) in the 3'UTR of the

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target mRNAs have the ability to disturb the miRNA binding by modifying the existing MREs or by new MREs creating [8]. The pathological importance of these functional SNPs has been studied in a variety of diseases [9], including neurodegenerative diseases [10]. Additionally, these SNPs in miRNA target sites make the pathway of this disease more complicated and result in some changes in phenotype. Also, they are regularly involved in the disease's susceptibility or onset [11]. Consequently, SNPs in miRNA binding sites might have main functions that can be applied for ADHD diagnosis and treatment. This study predicted miRNA target binding sites at 3'UTR of ADHD-implicated genes in order to identify SNPs, which could modify miRNA-target mRNA interactions, and also result in target gene expression modification.

2. MATERIALS AND METHODS

2.1. *In silico* Analysis of ADHD-associated Genes

ADHD-related genes and their pathways were achieved from ADHD gene [12] (http://adhd.psych.ac.cn/), DisGeNET [13], dbGaP (https://www.ncbi.nlm.nih.gov/gap/phegeni), Ovid (http://www.ovid.com), and DAVID Bioinformatics Resources 6.8 (https://david.ncifcrf.gov/).

2.2. Prediction of the SNPs at 3'UTR of Candidate Genes

The “database SNP” (http://www.ncbi.nlm.nih.gov/SNP/) was applied in order to identify the selected genes SNPs, and also the genetic variants at the 3'UTR were selected. Moreover, the allele's frequencies were investigated and the SNPs with the amount of minor allele frequency (MAF) higher than 0.05 in HapMap were chosen and documented.

2.3. The Computational Analysis of miRNA Binding Sites and the Calculation of the Binding Free Energy

miRNA target prediction databases including miRdSNP [14] (http://mirdsnp.ccr.buffalo.edu/search.php/), MirSNP [15] (http://202.38.126.151/hmdd/mirsnp/search/), TargetScan Human 6.2 [16] (http://www.targetscan.org), miRNASNP 2.0 [17] (http://www.bioguo.org/miRNASNP/search.php), and Poly miRTS 3.0 [18] (http://compbio.uthsc. edu/miRSNP/) were used, in order to identify putative miRNA target binding sites containing the 3'UTR SNPs of each selected gene associated with ADHD. miRNA sequences were attained from miRBase 21 (http://mirbase.org). The 3'UTR SNPs in the target gene have an effect on miRNA function. These variants could decrease, increase, break, and create a miRNA binding site [15]. The SNP sequence and the function were attained from MirSNP and investigating miRNA binding site, respectively.

The Gibbs binding free energy (ΔG, kCal/mol) was assessed for the major and the minor alleles using RNAcofold (http://rna.tbi.univie.ac.at/cgi-bin/RNAcofold.cgi). After that, the free energies difference (*i.e.* ΔΔG) was calculated between two alleles as “variation of ΔG”. The greater the difference (|ΔΔG|), the higher the stability of the mRNA: miRNA duplex. Moreover, SNPs with the energy less than 0.1 kCal/mol, consequently could perform weak activity [19].

3. RESULTS

3.1. Selection of ADHD: Associated Genes and SNPs

Different databases and electronic libraries including Ovid, PubMed, and Web of Science, were applied in order to select genes and SNPs. Also, 51 ADHA-implicated genes were found (Table **1**). After that, 124 SNPs were selected in the 3'UTR of 35 genes with MAF>0.05 as shown in Table **2**. About 61% of genes have more than one SNP.

3.2. The Prediction of SNPs Locating in the miRNAs Target Binding Site

This study investigated the 124 SNPs within 3'UTR of these 35 genes. The results demonstrated that 71 SNPs of 31 genes have the target binding sites for miRNA (Table **3**). 284 putative miRNAs were identified using different databases as followings: 283 miRNAs by the use of MirSNP, 10 miRNAs by TargetScan Human 6.2, 44 miRNAs using PolymiRTS 3.0, 19 miRNAs by the use of miRNASNP 2.0, and 6 miRNAs using miRdSNP, which they have been overlapped with each other. These SNPs have different effects on miRNA binding site including creation, break, increase, and decrease. Totally, 81 SNPs are MRE-creating (SNPs that create new MREs for miRNAs), 101 SNPs are MRE-breaking (SNPs that disrupt the miRNA binding sites completely), 61 SNPs are MRE-enhancing (SNPs that could increase the binding affinity of the miRNA to the binding sites), and finally, 41 SNPs are MRE-decreasing (SNPs that could decrease the miRNA binding efficacy to the binding sites) (Table **3**). Also, it is noteworthy to state that each SNP has a different, independent effect on each different miRNA, and that is, if one SNP is associated with four miRNAs, then it has four different effects. For example, the second SNP in Table **3** (rs3750625) has several different effects on mi-RNAs.

4. DISCUSSION

ADHD is identified as a disorder that has a neurobiological basis. Although the ADHD pathogenesis and etiology is still completely unidentified, family and molecular genetic studies results indicated the strong genetic influence on ADHD [20]. It has been also reported that SNPs in regulatory regions could affect the gene expression. They play a remarkable role in susceptibility to multifactorial diseases [21]. For example, two SNPs -1291C/G and rs1800544 of the Alpha-2A Adrenergic Receptor (ADRA2A) Gene was associated with the efficacy of methylphenidate for the treatment of ADHD subjects [22, 23]. The ADRA2A receptors expressed on prefrontal cortical pyramidal neurons play a significant role in the regulation of the prefrontal cortex function [24] and correlate to methylphenidate therapeutic effect [25].

In addition to the SNPs that could affect the amino acid sequence, regulatory SNPs in the genome non-coding sequences might also develop the phenotypic variation in humans. It has been indicated that the SNPs within 3'UTR may interfere with miRNAs and target genes binding, resulting in dysregulation of mRNA and protein [26], which will influence the susceptibility to ADHD. In fact, García-Martínez *et al.* (2016)

Table 1. The list of candidate genes to analyze the genetic variants at the 3'UTR.

Gene Name	Gene Symbol	Gene Name	Gene Symbol
Adrenoceptor alpha 2A	ADRA2A	Brain-derived neurotrophic factor	BDNF
Astrotactin2	ASTN2	Cholinergic Receptor, Nicotinic, Alpha 4 subunit	CHRNA4
Butyrylcholinesterase	BCHE	Ciliary neurotrophic factor	CNTF
Brain-derived neurotrophic factor	BDNF	Catechol-O-methyltransferase	COMT
Cholinergic Receptor, Nicotinic, Alpha 4 subunit	CHRNA4	5-Hydroxytryptamine receptor 3A	HTR3A
Ciliary neurotrophic factor	CNTF	Monoamine oxidase A	MAOA
Catechol-O-methyltransferase	COMT	Monoamine oxidase B	MAOB
Complexin 2	CPLX2	Nitric oxide synthase 1	NOS1*
Dopamine beta-hydroxylase	DBH	Protein kinase, cGMP-dependent, type I	PRKG1
Dopa decarboxylase	DDC	Solute Carrier Family 1 Member 3	SLC1A3
DIRAS family GTPase	DIRAS2	Solute Carrier Family 6 Member 2	SLC6A2/NET1
Dopamine receptor D1	DRD1	Solute Carrier Family 6 Member 3	SLC6A3/DAT1
Dopamine receptor D2/Ankyrin repeat and kinase domain containing 1	DRD2/ANNK1	Solute Carrier Family 6 Member 4	SLC6A4/5HTT
Dopamine receptor D5	DRD5	Solute Carrier Family 9 Member 9	SLC9A9/NHE9
Fatty acid desaturase 2	FADS2	Solute Carrier Family 18 Member2	SLC18A2/VMAT2
Glial cell derived neurotrophic factor	GDNF	Synaptosome associated protein 25	SNAP25
Glutamat ionotropic receptor NMDA type subunit 2A	GRIN2A	Sparc/osteonectin, cwcv and kazal-like domains proteoglycan 3	SPOCK3
Glutamate metabotropic receptor 7	GRM7	Syntaxin1A	STX1A
5-Hydroxytryptamine receptor 1A	HTR1A	Synaptophysin	SYP
5-Hydroxytryptamine receptor 1B	HTR1B	Synaptotagmin I	SYT1
5-Hydroxytryptamine receptor 1E	HTR1E	Transcription elongation regulator 1-like	TCERG1L
5-Hydroxytryptamine receptor 2A	HTR2A	Tryptophan hydroxylase 2	TPH2
5-Hydroxytryptamine receptor 2C	HTR2C	Vesicle-associated membrane protein 2	VAMP2
Adrenoceptor alpha 2A	ADRA2A	5-Hydroxytryptamine receptor 3A	HTR3A
Butyrylcholinesterase	BCHE	-	-

Table 2. The list of candidate genes associated with ADHD and SNPs with MAFs higher than 0.05.

Gene Symbol	dbSNP ID	Variation	MAF
ADRA2A	Rs11195419	C/A	0.1813
-	Rs553668	A/G, T	0.3295
-	Rs3750625	C/A	0.1336
-	Rs13306146	A/G	0.1372
ASTN2	Rs7518	C/T	0.2005
BCHE	Rs3495	C/A, T	0.3522

Table 2. Contd…

Gene Symbol	dbSNP ID	Variation	MAF
BDNF	Rs7124442	C/T, G	0.3299
CHRNA4	Rs6090378	A/G	0.0677
-	Rs6011770	C/T	0.0623
-	Rs2236196	G/A, C	0.3858
CNTF	Rs2515362	T/C	0.4874
COMT	Rs165599	G/A	0.4908
-	Rs165728	C/T, G	0.1593
CPLX2	Rs3822674	T/C	0.4984
-	Rs11747985	G/A, C	0.4087
-	Rs1006101	T/C	0.4639
-	Rs4867809	A/G	0.4349
-	Rs1560034	T/C	0.3249
DBH	Rs129882	C/T	0.2554
-	Rs13306304	G/A, C	0.0857
DDC	Rs11575553	G/A	0.0769
DIRAS2	Rs7854469	T/A, C	0.1392
-	Rs1542478	A/G	0.0527
-	Rs16906711	C/G	0.1122
-	Rs726214	G/A	0.1767
DRD1	Rs4867798	T/C	0.3329
-	Rs686	G/A	0.3950
DRD2/ANNK1	Rs6278	C/A	0.2041
-	Rs6274	A/T, C	0.0551
-	Rs6279	G/C	0.4782
-	Rs6276	C/T	0.4669
DRD5	Rs1967551	T/C	0.4255
GDNF	Rs17379771	C/T, A	0.2350
-	Rs11111	T/C	0.2476
-	Rs3749692	A/G	0.4601
GRIN2A	Rs767749	T/G	0.2494
-	Rs1420040	A/G	0.4233
-	Rs9940680	G/C	0.4163
-	Rs9933624	T/A, C	0.4173
-	Rs8045712	C/T	0.3676
-	Rs8044472	G/A, C	0.2478
-	Rs1014531	G/A	0.2682
HTR1A	Rs878567	A/C, G	0.3522

Table 2. Contd…

Gene Symbol	dbSNP ID	Variation	MAF
-	Rs6449693	G/A	0.3512
HTR1B	Rs13212041	C/T	0.2847
-	Rs6297	C/A, T	0.0765
HTR1E	Rs11970489	T/C	0.1841
-	Rs11963460	A/T, C	0.1879
-	Rs11964260	A/C	0.1859
HTR2A	Rs7323441	A/T	0.0891
-	Rs7325168	T/C	0.0887
-	Rs7324017	C/T	0.2314
-	Rs7324218	C/T	0.0887
-	Rs9595552	T/G	0.0927
-	Rs3803189	T/G	0.1843
-	Rs3125	C/G, T	0.1260
HTR2C	Rs1801412	T/G	0.0628
HTR3A	Rs1150219	G/C	0.0940
MAOA	Rs3027407	A/G	0.4490
MAOB	Rs3027438	A/G, T	0.1015
-	Rs3027439	A/G	0.1340
-	Rs2072745	A/T	0.1338
-	Rs3027440	A/G	0.1009
-	Rs17462	T/C	0.0630
NOS1	Rs12425729	T/C	0.1136
-	Rs10774906	T/C	0.4746
-	Rs10774907	G/A	0.4738
-	Rs1105026	A/G, T	0.1446
-	Rs9658570	G/T	0.0911
-	Rs9658562	A/T	0.0673
-	Rs11068415	G/C, T	0.1368
-	Rs2682826	G/A	0.2558
SLC1A3	Rs1049522	A/C	0.3504
-	Rs2269272	C/T	0.2049
SLC6A2	Rs42879	T/C	0.0739
-	Rs36006	T/C	0.0741
SLC6A3	Rs7732456	A/C, T	0.0609
-	Rs3797200	C/G, T	0.1773
-	Rs27072	C/T, A	0.2051
-	Rs1042098	A/G	0.2951

Table 2. Contd…

Gene Symbol	dbSNP ID	Variation	MAF
SLC6A4	Rs7224199	G/T	0.4189
-	Rs3813034	A/C	0.4834
-	Rs1042173	A/C	0.4852
SLC9A9	Rs3796229	A/G	0.1326
-	Rs3796228	T/C	0.0871
-	Rs3796227	G/C, T	0.0609
SLC18A2	Rs10377	A/C	0.4521
-	Rs14240	T/C, A	0.4523
-	Rs363282	G/A	0.3091
-	Rs363235	T/A, C	0.3089
-	Rs363236	C/T, A	0.3091
-	Rs363237	T/A, C	0.4519
-	Rs363238	C/A	0.2218
SNAP25	Rs3746544	G/T	0.2812
-	Rs1051312	T/C	0.1256
-	Rs8636	T/A, C	0.2538
SPOCK3	Rs6846930	C/G, A	0.3966
-	Rs3762245	A/G	0.2081
STX1A	Rs867500	G/T, A, C	0.2314
-	Rs1569061	C/T	0.0931
SYP	Rs7889267	G/A	0.1399
SYT1	Rs1245667	T/C	0.1062
-	Rs2248102	G/A	0.0545
TCERG1L	Rs2944507	A/G	0.2296
-	Rs2280200	A/T	0.3720
-	Rs2280199	C/G, T	0.4780
-	Rs1055043	T/C	0.3217
-	Rs2918092	G/A	0.1502
TPH2	Rs17110747	G/A	0.1454
VAMP2	Rs1150	A/G	0.3652
-	Rs1061032	T/A, C, G	0.2598
-	Rs8636	T/C, A	0.2538
SPOCK3	Rs6846930	C/G, A	0.3966
-	Rs3762245	A/G	0.2081
STX1A	Rs867500	G/T, A, C	0.2314
-	Rs1569061	C/T	0.0931
SYP	Rs7889267	G/A	0.1399

Table 2. Contd…

Gene Symbol	dbSNP ID	Variation	MAF
SYT1	Rs1245667	T/C	0.1062
-	Rs2248102	G/A	0.0545
TCERG1L	Rs2944507	A/G	0.2296
-	Rs2280200	A/T	0.3720
-	Rs2280199	C/G, T	0.4780
-	Rs1055043	T/C	0.3217
-	Rs2918092	G/A	0.1502
TPH2	Rs17110747	G/A	0.1454
VAMP2	Rs1150	A/G	0.3652
-	Rs1061032	T/A, C, G	0.2598
-	Rs8636	T/A, C	0.2538
SPOCK3	Rs6846930	C/G, A	0.3966
-	Rs3762245	A/G	0.2081
STX1A	Rs867500	G/T, A, C	0.2314
-	Rs1569061	C/T	0.0931
SYP	Rs7889267	G/A	0.1399
SYT1	Rs1245667	T/C	0.1062
-	Rs2248102	G/A	0.0545
TCERG1L	Rs2944507	A/G	0.2296
-	Rs2280200	A/T	0.3720
-	Rs2280199	C/G, T	0.4780

Table 3. Predicted SNPs and miRNAs analyzing using miRNA target prediction databases.

Gene	dbSNP ID	Variation	miRNA	|ΔΔG| (kCal/mol)	MirSNP	TagetScan	PolymiRTS	miRNASNP	miRdSNP	Effect
ADRA2A	rs11195419	C/A	hsa-miR-3677-5p	6.85	+	+	+			Create
			hsa-miR-3926	2.2	+	+	+			Create
			hsa-miR-548s	0.43	+	+	+			Create
	rs3750625	C/A	hsa-miR-1207-5p	0.05	+	+	+			Create
			hsa-miR-149-3p	1.56	+					Enhance
			hsa-miR-2682-5p	6.44	+		+			Break
			hsa-miR-3150a-3p	0.02	+					Enhance
			hsa-miR-34a-5p	1.38	+		+	+		Break
			hsa-miR-34b-5p	1.5	+		+	+		Break
			hsa-miR-34c-5p	1.56	+		+	+	+	Break
			hsa-miR-3616-3p	0.32	+					Decrease

Table 3. Contd…

Gene	dbSNP ID	Variation	miRNA	|ΔΔG| (kCal/mol)	MirSNP	TagetScan	PolymiRTS	miRNASNP	miRdSNP	Effect
			hsa-miR-4446-3p	2.99	+	+	+			Create
			hsa-miR-449a	0.0	+		+	+	+	Break
			hsa-miR-449b-5p	3.29	+		+	+		Break
			hsa-miR-449c-5p	1.11	+		+	+		Break
			hsa-miR-4514	0.0	+					Enhance
			hsa-miR-4692	0.0	+					Decrease
			hsa-miR-4763-3p	0.98	+	+				Create
			hsa-miR-512-3p	2.74	+		+	+		Break
			hsa-miR-940	0.44	+	+	+	+		Create
	rs13306146	A/G	hsa-miR-432-5p	0.37	+					Decrease
			hsa-miR-646	0.16	+	+				Break
ASTN2	rs7518	C/T	hsa-miR-3189-3p	0.3	+		+			Break
			hsa-miR-5001-3p	2.34	+					Enhance
			hsa-miR-5089	0.01	+					Break
BDNF	rs7124442	C/T, G	hsa-miR-142-5p	0.65	+					Decrease
			hsa-miR-5590-3p	0.1	+					Enhance
			hsa-miR-922	0.77	+					Break
CHRNA4	rs6090378	A/G	hsa-miR-136-5p	0.36	+					Break
	rs6011770	C/T	hsa-miR-3186-3p	0.23	+					Enhance
			hsa-miR-4267	0.04	+					Break
			hsa-miR-4661-5p	0.77	+					Create
			hsa-miR-629-3p	0.14	+					Decrease
CNTF	rs2515362	T/C	hsa-miR-3174	0.33	+					Enhance
			hsa-miR-548ac	0.94	+					Break
			hsa-miR-548d-3p	0.35	+					Break
			hsa-miR-548h-3p	0.9	+					Break
			hsa-miR-548z	0.84	+					Break
COMT	rs165728	C/T, G	hsa-miR-3138	0.4	+					Create
			hsa-miR-4520a-3p	1.59	+					Create
			hsa-miR-541-3p	1.52	+	+				Break
			hsa-miR-654-5p	1.76	+	+				Break
CPLX2	rs3822674	T/C	hsa-miR-4287	0.22	+					Enhance
			hsa-miR-4685-3p	0.22	+					Enhance
			hsa-miR-498	0.24	+					Break
	rs1006101	T/C	hsa-miR-3689d	2.89	+	+				Create
			hsa-miR-4802-5p	1.85	+	+				Create
			hsa-miR-588	2.9	+					Decrease
			hsa-miR-609	2.9	+					Break

Table 3. Contd…

Gene	dbSNP ID	Variation	miRNA	|ΔΔG| (kCal/mol)	MirSNP	TagetScan	PolymiRTS	miRNASNP	miRdSNP	Effect
	rs4867809	A/G	hsa-miR-4471	0.09	+		+			Create
			hsa-miR-892b	0.1	+		+	+		Create
	rs1560034	T/C	hsa-miR-4435	0.09	+					Create
			hsa-miR-548s	0.39	+					Break
DBH	rs129882	C/T	hsa-miR-1268a	1.79	+	+				Break
			hsa-miR-1268b	1.68	+	+				Break
			hsa-miR-1285-3p	0.98	+			+		Create
			hsa-miR-3187-5p	1.69	+					Create
			hsa-miR-4253	2.13	+					Create
			hsa-miR-4486	0.35	+	+				Break
			hsa-miR-5189	0.03	+					Create
			hsa-miR-612	0.36	+			+		Create
	rs1330630	G/A, C	hsa-miR-1908	0.13	+					Decrease
			hsa-miR-3180	0.02	+					Enhance
			hsa-miR-3180-3p	0.07	+					Enhance
			hsa-miR-3196	2.77	+					Enhance
			hsa-miR-4697-5p	0.01	+	+	+			Enhance
			hsa-miR-4787-5p	0.34	+		+			Break
			hsa-miR-609	0.01	+		+			Break
DIRAS2	rs7854469	T/A,C	hsa-miR-3163	0.07	+		+			Decrease
			hsa-miR-374a-5p	0.09	+		+			Create
			hsa-miR-374b-5p	0.18	+		+			Create
	rs16906711	C/G	hsa-miR-139-5p	0.28	+		+	+		Break
			hsa-miR-633	0.4	+					Create
	rs726214	G/A	hsa-miR-3117-3p	2.43	+					Create
			hsa-miR-3169	0.1	+					Create
			hsa-miR-3199	0.18	+	+				Break
			hsa-miR-4648	2.29	+	+				Break
			hsa-miR-4692	0.14	+					Decrease
DRD1	rs686	G/A	hsa-miR-4323	0.45	+					Create
DRD2/ANNK1	rs6278	C/A	hsa-miR-214-3p	1.58	+	+	+			Break
			hsa-miR-298	1.3	+		+			Create
			hsa-miR-3154	2.16	+		+			Create
			hsa-miR-3619-5p	1.82	+	+	+			Break
			hsa-miR-3714	4.48	+					Decrease
			hsa-miR-3918	0.92	+					Enhance
			hsa-miR-761	1.59	+	+	+			Break

Table 3. Contd…

Gene	dbSNP ID	Variation	miRNA	|ΔΔG| (kCal/mol)	MirSNP	TagetScan	PolymiRTS	miRNASNP	miRdSNP	Effect
	rs6279	G/C	hsa-miR-4311	0.31	+	+				Break
			hsa-miR-4323	1.31	+					Enhance
			hsa-miR-4758-3p	1.85	+					Enhance
	rs6276	C/T	hsa-miR-1234	0.69	+	+				Create
			hsa-miR-3064-5p	0.42	+					Break
			hsa-miR-3176	0.03	+		+			Break
			hsa-miR-3922-3p	0.8	+		+			Break
			hsa-miR-4316	0.68	+					Decrease
			hsa-miR-4710	0.08	+					Decrease
			hsa-miR-485-5p	5.2	+					Enhance
			hsa-miR-5580-5p	0.02	+		+			Break
DRD5	rs1967551	T/C	hsa-miR-210	0.58	+					Enhance
			hsa-miR-4697-3p	0.41	+					Create
			hsa-miR-636	0.3	+					Enhance
			hsa-miR-654-3p	0.15	+					Break
GDNF	rs11111	T/C	hsa-let-7f-2-3p	2.29	+		+			Create
			hsa-miR-1185-1-3p	3.66	+		+			Create
			hsa-miR-1185-2-3p	3.69	+		+			Create
			hsa-miR-3934	0.75	+					Enhance
	rs3749692	A/G	hsa-let-7a-2-3p	0.69	+			+		Break
			hsa-let-7g-3p	0.65	+			+		Break
			hsa-miR-1915-3p	0.45	+					Enhance
			hsa-miR-3649	2.81	+					Create
			hsa-miR-4700-3p	2.22	+					Break
			hsa-miR-5685	2.81	+					Enhance
GRIN2A	rs767749	T/G	hsa-miR-3618	1.84	+					Break
	rs1420040	A/G	hsa-miR-4645-5p	0.37	+					Decrease
			hsa-miR-580	0.15	+					Create
	rs9940680	G/C	hsa-miR-181a-5p	2.91	+					Decrease
			hsa-miR-181b-5p	1.31	+					Enhance
			hsa-miR-181d	3.91	+					Enhance
			hsa-miR-3663-5p	4.64	+					Break
	rs9933624	T/A, C	hsa-miR-22-5p	0.45	+					Enhance
			hsa-miR-607	0.71	+					Create

Table 3. Contd…

Gene	dbSNP ID	Variation	miRNA	|ΔΔG| (kCal/mol)	MirSNP	TagetScan	PolymiRTS	miRNASNP	miRdSNP	Effect
	rs8045712	C/T	hsa-miR-1343	0.29	+					Decrease
	rs8044472	G/A, C	hsa-miR-4637	0.09	+					Decrease
			hsa-miR-4653-3p	0.04	+					Create
			hsa-miR-520a-5p	0.14	+			+		Break
			hsa-miR-525-5p	0.13	+			+		Break
	rs1014531	G/A	hsa-miR-1185-5p	1.44	+					Enhance
			hsa-miR-1266	1	+					Create
			hsa-miR-197-5p	1	+					Create
			hsa-miR-3132	0.99	+					Create
			hsa-miR-3664-3p	1.04	+					Break
			hsa-miR-3679-5p	1.02	+					Enhance
			hsa-miR-4518	1.87	+					Create
			hsa-miR-510	1	+					Decrease
HTR2A	rs3125	C/G, T	hsa-miR-3662	0.08	+					Decrease
			hsa-miR-3976	2.92	+		+			Break
			hsa-miR-5689	0.2	+	+	+			Create
HTR2C	rs1801412	T/G	hsa-miR-10a-5p	0.4	+			+		Break
			hsa-miR-10b-5p	2.66	+			+		Break
			hsa-miR-141-3p	4.61	+			+		Create
			hsa-miR-200a-3p	4.6	+			+		Create
			hsa-miR-2054	0.86	+					Decrease
			hsa-miR-2115-3p	1.62	+					Enhance
			hsa-miR-339-5p	5.82	+			+		Break
MAOA	rs3027407	A/G	hsa-miR-3120-5p	2.49	+		+			Create
			hsa-miR-4652-3p	0.22	+	+	+			Break
MAOB	rs3027439	A/G	hsa-miR-3173-3p	0.1	+			+		Create
			hsa-miR-3689d	0.2	+					Create
			hsa-miR-4668-5p	0.18	+					Decrease
			hsa-miR-4668-5p	0.18	+					Enhance
			hsa-miR-4668-5p	0.18	+					Enhance
			hsa-miR-583	0.03	+					Break
	rs2072745	A/T	hsa-miR-4511	0.01	+					Enhance
	rs3027440	A/G	hsa-miR-1226-5p	0.0	+					Decrease
			hsa-miR-3616-3p	0.02	+					Break
			hsa-miR-4744	0.04	+					Enhance
	rs17462	T/C	hsa-miR-4299	0.47	+	+				Break
			hsa-miR-4738-3p	0.84	+	+	+			Break
			hsa-miR-582-3p	0.7	+	+				Break

Table 3. Contd…

Gene	dbSNP ID	Variation	miRNA	|ΔΔG| (kCal/mol)	MirSNP	TagetScan	PolymiRTS	miRNASNP	miRdSNP	Effect
NOS1	rs12425729	T/C	hsa-miR-548v	0.97	+					Decrease
	rs10774906	T/C	hsa-miR-4752	1.47	+					Create
			hsa-miR-548v	1.46	+					Enhance
	rs10774907	G/A	hsa-miR-3145-3p	0.81	+			+		Break
			hsa-miR-452-5p	0.83	+					Decrease
	rs9658570	G/T	hsa-miR-3120-5p	0.04	+					Enhance
			hsa-miR-632	0.05	+					Decrease
	rs9658562	A/T	hsa-miR-302b-5p	1.56	+	+				Create
			hsa-miR-302c-5p	0.35	+	+				Create
			hsa-miR-302d-5p	0.29	+	+				Create
			hsa-miR-3143	0.17	+	+				Create
			hsa-miR-593-5p	0.06	+					Enhance
	rs2682826	G/A	hsa-miR-140-5p	2.17	+					Enhance
			hsa-miR-29b-2-5p	0.6	+					Decrease
			hsa-miR-501-3p	2.03	+					Decrease
			hsa-miR-502-3p	2.07	+					Decrease
SLC1A3	rs1049522	A/C	hsa-miR-3171	0.0	+	+	+			Break
			hsa-miR-3668	0.0	+		+			Create
			hsa-miR-576-3p	0.19	+		+			Create
SLC6A2	rs42879	T/C	hsa-miR-30a-3p	2.73	+					Enhance
			hsa-miR-30d-3p	4.22	+					Enhance
			hsa-miR-4263	1.53	+					Break
			hsa-miR-4329	3.34	+					Create
			hsa-miR-4786-5p	0.49	+					Create
			hsa-miR-5693	2.68	+					Enhance
	rs36006	T/C	hsa-miR-3692-3p	0.13	+					Break
			hsa-miR-4311	0.12	+					Break
SLC6A3	rs7732456	A/C, T	hsa-miR-3976	1.86	+					Break
			hsa-miR-4427	1.92	+					Decrease
			hsa-miR-5186	1.92	+					Break
			hsa-miR-5585-3p	1.51	+					Enhance
	rs1042098	A/G	hsa-miR-187-3p	3.05	+					Enhance
			hsa-miR-2116-3p	0.44	+					Enhance
			hsa-miR-4713-5p	2.45	+					Enhance
			hsa-miR-5187-5p	2.28	+					Break

Table 3. Contd…

Gene	dbSNP ID	Variation	miRNA	|ΔΔG| (kCal/mol)	MirSNP	TagetScan	PolymiRTS	miRNASNP	miRdSNP	Effect
SLC6A4	rs7224199	G/T	hsa-miR-1252	0.03	+					Break
			hsa-miR-3185	0.09	+					Break
	rs3813034	A/C	hsa-miR-2053	0.37	+					Break
			hsa-miR-569	0.42	+					Break
			hsa-miR-571	0.31	+					Decrease
	rs1042173	A/C	hsa-miR-3163	0.71	+					Enhance
			hsa-miR-3942-5p	0.1	+					Enhance
SLC9A9	rs3796229	A/G	hsa-miR-15a-3p	0.62	+					Decrease
			hsa-miR-1972	0.34	+					Enhance
	rs3796228	T/C	hsa-miR-1260a	5.37	+		+			Create
			hsa-miR-1260b	0.38	+		+			Create
SLC18A2	rs10377	A/C	hsa-miR-3145-3p	0.78	+					Enhance
			hsa-miR-3163	3.11	+					Enhance
			hsa-miR-3163	3.11	+					Enhance
			hsa-miR-3646	3.12	+			+		Create
			hsa-miR-3662	3.28	+		+	+		Create
	rs14240	T/C, A	hsa-miR-1297	1.98	+		+			Break
			hsa-miR-26a-5p	2.26	+		+	+		Break
			hsa-miR-26b-5p	2.27	+		+			Break
			hsa-miR-3671	1.87	+	+	+			Create
			hsa-miR-4465	1.48	+		+			Break
			hsa-miR-5002-5p	2.32	+					Decrease
			hsa-miR-607	1.8	+	+	+			Create
	rs363282	G/A	hsa-miR-2278	2.64	+					Decrease
	rs363235	T/A, C	hsa-miR-1205	0.97	+					Enhance
			hsa-miR-125b-2-3p	3.2	+		+	+		Create
			hsa-miR-1297	0.83	+		+			Break
			hsa-miR-26a-5p	1	+		+	+		Break
			hsa-miR-26b-5p	0.82	+		+	+		Break
			hsa-miR-4320	2.51	+					Break
			hsa-miR-4418	1.35	+					Enhance
			hsa-miR-4465	0.7	+		+			Break
			hsa-miR-509-3-5p	0.41	+					Enhance
			hsa-miR-509-5p	0.78	+					Enhance
			hsa-miR-513b	1.4	+					Create
			hsa-miR-513c-5p	3.87	+		+	+		Break
			hsa-miR-514b-5p	4.36	+		+	+		Break

Table 3. Contd…

Gene	dbSNP ID	Variation	miRNA	|ΔΔG| (kCal/mol)	MirSNP	TagetScan	PolymiRTS	miRNASNP	miRdSNP	Effect
	rs363238	C/A	hsa-miR-297	0.77	+					Decrease
			hsa-miR-3149	0.98	+			+		Break
			hsa-miR-4677-5p	0.53	+		+			Decrease
			hsa-miR-4774-5p	6.41	+	+				Create
			hsa-miR-578	0.98	+		+	+		Break
			hsa-miR-643	0.98	+			+		Break
SNAP25	rs3746544	G/T	hsa-miR-3617	0.56	+					Break
			hsa-miR-3913-3p	0.14	+					Break
			hsa-miR-641	0.38	+					Break
	rs1051312	T/C	hsa-miR-3646	0.31	+					Decrease
			hsa-miR-3664-3p	0.24	+		+			Break
			hsa-miR-510	1.86	+				+	Break
	rs8636	T/A, C	hsa-miR-103b	3.34	+	+	+			Create
			hsa-miR-424-3p	1.78	+		+	+		Break
			hsa-miR-515-5p	0.22	+					Enhance
			hsa-miR-519e-5p	0.66	+					Decrease
SPOCK3	rs6846930	C/G, A	hsa-miR-495	0.32	+					Break
			hsa-miR-5688	0.33	+					Break
	rs3762245	A/G	hsa-miR-4260	0.05	+					Decrease
			hsa-miR-499b-5p	2.59	+		+			Break
STX1A	rs1569061	C/T	hsa-miR-3173-5p	4.34	+					Enhance
			hsa-miR-661	0.0	+					Enhance
SYP	rs7889267	G/A	hsa-miR-1266	0.11	+					Decrease
			hsa-miR-1321	0.14	+					Create
			hsa-miR-149-3p	0.0	+			+		Create
			hsa-miR-3173-3p	0.18	+			+		Break
			hsa-miR-4270	0.16	+					Create
			hsa-miR-4441	0.06	+					Create
			hsa-miR-4518	0.1	+					Decrease
			hsa-miR-4728-5p	0.02	+					Create
			hsa-miR-4739	2.12	+					Create
			hsa-miR-4756-5p	0.18	+					Create
			hsa-miR-4779	0.0	+					Break

Table 3. Contd…

Gene	dbSNP ID	Variation	miRNA	|ΔΔG| (kCal/mol)	MirSNP	TagetScan	PolymiRTS	miRNASNP	miRdSNP	Effect
SYT1	rs1245667	T/C	hsa-miR-143-5p	1.25	+	+	+	+		Create
			hsa-miR-148a-3p	1.17	+	+	+	+		Create
			hsa-miR-148b-3p	0.83	+	+	+	+		Create
			hsa-miR-152	1.35	+	+			+	Create
			hsa-miR-3189-3p	1.85	+					Decrease
			hsa-miR-34c-5p	1.46	+				+	Enhance
			hsa-miR-449a	1.47	+				+	Enhance
			hsa-miR-449b-5p	1.47	+					Enhance
			hsa-miR-4650-3p	1.78	+		+			Break
			hsa-miR-635	0.72	+					Enhance
			hsa-miR-936	1.3	+	+	+			Create
	rs2248102	G/A	hsa-miR-4327	3.67	+		+			Break
VAMP2	rs1150	A/G	hsa-miR-5583-3p	0.0	+					Enhance
			hsa-miR-601	0.0	+					Create
	rs1061032	T/A, C, G	hsa-miR-127-3p	0.02	+					Decrease
			hsa-miR-149-3p	2.7	+					Create
			hsa-miR-4447	2.56	+	+				Break
			hsa-miR-4472	2.12	+	+				Break
			hsa-miR-4481	1.76	+	+				Break
			hsa-miR-4728-5p	2.47	+					Create
			hsa-miR-4745-5p	3.53	+	+				Break

demonstrated that an SNP (rs4938723) located in the promoter region of the pri-miR-34b/c could affect the binding of transcription factor GATA, and consequently, result in a reduction of the miR-34b and miR-34c expression levels in PBMCs of ADHD patients [27].

Up to date, there have been a few investigations conducted on miRNAs in ADHD. Wu *et al*. (2015) demonstrated that the miRNA let-7d expression was increased in the patient's group serum [28]. In addition, Srivastav *et al*. (2018) reported that miRNAs could regulate the expression of DAT1, SNAP-25, HTR2C, BDNF, HTR1B, and those genes associated with ADHD etiology. miRNAs dysregulation influences the genes regulation mechanisms, which could affect neurodevelopmental processes, and also investigating the role of miRNAs in ADHD appears to be a promising step in understanding its etiology [29]. In addition, Kandemir *et al.* (2014) indicated that the miRNA 155a-5p levels were increased in ADHD subjects, and the levels of miRNA 18a-5p, 22-3p, 24-3p, 106b-5p, and 107 were significantly decreased in patients [30].

In this study, 284 miRNAs were predicted, and amongst them were several miRNAs that were investigated in earlier studies, but they were not the studies in the field of ADHD. For example, the binding ability of hsa-mir-1207-5p appears to be affected, due to the rs13385 (C1936T) SNP presence in the 3′UTR of HBEGF. The 1936C allele at the hsa-miR-1207-5p binding site is associated with HBEGF down-regulation and a less severe phenotype of CFHR5 nephropathy (a monogenic renal disorder). In contrast, the 1936T allele reduces the hsa-mir-1207-5p binding ability that would result in enhanced HBEGF expression and also the disorder's severe phenotype [31].

miR-149-3p plays dual roles in different cancer types. MiR-149-3p targets the GSK3α, which leads to apoptosis decrease in melanoma cells. miR-149-3p has also the ability to reduce apoptosis and promote proliferation in T-cell acute lymphoblastic leukemia (T-ALL). In addition, miR-149-3p overexpression was reported in liver and ovarian cancer cell lines after performing bafilomycin A1 treatment [32].

Gallelli *et al*. (2019) found the hsa-miR-34a-5p enhanced expression in both untreated migraine patients' saliva and serum, in comparison with both treated migraine patients and healthy controls that proposing an hsa-miR-34a-5p potential role as a predictive biomarker for the therapeutic response in central nervous system pathological processes [33]. More-

over, hsamiR-34a-5p dysregulation was reported in schizophrenia prefrontal cortex samples; while its expression was enhanced upon lithium treatment. Therefore, hsa-miR-34a-5p was recommended for schizophrenia predicting [34].

In one study, hsa-miR-432-5p appears to predict Schizophrenia and its clinical symptoms [35].

The miR-646 expression levels decreased in tumor tissues, and along with that in metastatic renal cell carcinoma. Actually, miR-646 controlled the NOB1 negatively and repressed the renal cancer cell migration and proliferation throughout MAPK pathway [36]. Other miRNAs including miR-3189-3p [37], hsa-miR-142-5p [38, 39], has-miR-3617 [40], and miR-143-5p were also examined in different diseases [41].

Therefore, understanding the ADHD associated miRNAs-target genes interactions in neurodevelopment and neural function are not only important for the ADHD etiology but also can affect the diagnosis, prognosis, and treatment of ADHD.

Most of the previous investigations have evaluated the association between genes and their SNPs with ADHD; however, nowadays it is very significant for identifying the different genetic polymorphisms within miRNA binding sites of the ADHD-related genes. This study identified the ADHD-associated genes and their 3'UTR polymorphisms. Although, a large number of SNPs were investigated in the 3'UTR of 51 genes, which were predicted to have association with ADHD, but at the end most SNPs with MAF ≤ 0.05 or without HapMap data were excluded from this study, and only 124 SNPs in the 3'UTR of 35 genes were selected in order to be investigated.

miRNAs involved in the post-transcriptional regulation could recognize the target mRNAs by binding to MRE-sequences within the target genes 3'UTR [42]. Genetic variants within the binding site can influence the miRNAs function by target sites disrupting or creating [15]. These MRE-SNPs can modify the miRNA:MRE interaction, therefore, may be a regulatory mechanism underlying the gene expression, and could be involved in predisposition, inter-individual variation in ADHD gene expression, pathogenesis, and heterogeneity.

CONCLUSION

In conclusion, this study results recommended that SNPs within MRE of the genes might confer susceptibility risk to ADHD and contribute to ADHD heterogeneity, and phenotypic variability. As a result, SNPs within miRNAs binding sites result in better ADHD mechanism perception, and consequently better diagnostic, prognostic, or therapeutic tools. However, predicted SNPs into 3'UTR and miRNAs were just theoretical and further studies in regard are required in order to validate the function of these candidate genetic polymorphisms.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

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

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The authors confirm that the data supporting the findings of this research are available within the article.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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