Understanding miRNA Based Gene Regulation in Parkinson's Disease: An *in silico* Approach

Surya Narayan Rath[1,2], Manorama Patri[2*]

[1]*Department of Bioinformatics, Centre for Post Graduate Studies*
Odisha University of Agriculture and Technology
Bhubaneswar, Odisha, India
E-mail: snrbioinfo@gmail.com

[2]*Neurobiology Laboratory, Department of Zoology*
School of Life Sciences, Ravenshaw University
Cuttack, Odisha, India
E-mail: mpatri@ravenshawuniversity.ac.in

[*]*Corresponding author*

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Abstract: *Parkinson's disease (PD) is the second most common neurodegenerative disorder, mainly characterized by depletion or insufficient release of dopaminergic neurons in substantia nigra of the midbrain. Literature studies revealed the role of some protein coding genes such as LRRK2, SNCA, DJ-1, and Parkin in the disease pathway of PD and are regulated by few micro RNAs (miRNAs). miRNAs are highly conserved non-coding single stranded RNAs (~18-22bp) that target mRNA at 3'UTR (un-translated region) of protein coding genes and act as natural inhibitors. In spite of many researches, miRNAs based gene regulation in PD is still less understood. Therefore, the networks of miRNAs involved in normal development and survival of distinct neuronal populations, which are vulnerable in PD need to be addressed. Argonaute (AGO) protein is a family of protein, which assists miRNAs to bind with mRNAs of the target genes. The current study was undergone to elucidate the binding mechanism between AGO protein and miRNAs, and also with miRNAs-mRNAs duplex at atomic level by implicating computational approach. Therefore, thirty one miRNAs and twenty three different target genes involved in PD pathology were selected from public database and literatures. In silico analysis predicted strong binding affinity between three miRNAs such as miR-27b, miR-124-3p, and miR-29a with mRNAs of CYP1B1 and CDC42 genes respectively which may be considered as potent factors in gene regulation. The current investigation throws light towards understanding miRNAs based gene silencing mechanism in PD.*

Keywords*: miRNAs, Neurodegenerative disorders, Parkinson's disease, Argonaute, Dopaminergic neurons.*

Introduction

Progressive loss of dopaminergic neurons in an area of the midbrain known as substantia nigra causes Parkinson's disease (PD). PD is the second most common neurodegenerative disorder after Alzheimer's disease which is clinically characterized by resting tremor, rigidity, bradykinesia and postural instability [9]. PD also affects emotions and thinking ability. Some affected individuals develop psychiatric conditions such as depression and visual hallucinations. Moreover, there is a wide variation in the age of motor onset (ranging from age 20 to 90), with young-onset (before age 50) and representing 5-10% of PD cases [9]. The exact cause of PD is unknown, although some cases of PD are hereditary and occurred due to specific genetic mutations. In this context, microRNA (miRNA) profile of PD brains may offer insight into the molecular and pathological mechanisms of the disease.

miRNAs are highly conserved non-coding single stranded RNAs (~18-22bp) which target mRNA at 3'UTR (un-translated region) of the protein coding genes and act as natural inhibitor. These miRNAs participate in several biological processes such as cell differentiation, proliferation, and apoptosis and also regulates the expression of many genes [13, 17]. Therefore, miRNAs may be used as natural targets to prevent and control many severe diseases [5, 6, 13]. Few miRNAs (Table 1) are well characterized in PD due to their involvement in regulation of PD associated genes [9, 2-4, 7, 8, 10, 12, 16]. Significant role of miRNAs in vertebrate neuron development have been identified and particularly miR-133b found to have a critical role in dopaminergic neuron development in the midbrain [6, 16]. Several *in silico* approaches have been successfully used to integrate the knowledge of miRNAs and their target genes which may be useful to understand more about PD pathology. As a result, the knowledge of miRNAs which regulate PD associated genes such as ASYN, DJ-1, LRRK2, and PINK1 is well established [16]. Although the role miRNAs in PD gene regulation is well known, but the molecular mechanism of miRNAs induced gene silencing is still blurred [5, 13]. Therefore, study of interaction between miRNAs and their target genes at atomic level is crucial.

The present work is planned to develop a strategy for selection of suitable miRNAs, and their target genes associated with PD pathology. During hybrid formation between miRNAs-mRNA, a class of protein known as Argonaute (AGO) plays a significant role for assisting miRNAs to their target genes [5, 13]. Therefore *in silico* approach was applied to study the interaction between miRNAs, AGO and their target genes at molecular level. This study would throw light on miRNAs based gene regulation in PD.

Materials and methods

Selection of miRNAs and their target genes

Thirty one miRNAs and twenty three target genes in PD were taken from literatures [9, 2-4, 7, 8, 10, 12, 16]. The sequences of miRNAs-mRNA duplexes along with their binding affinity were inspected using miRTarbase web server (http://mirtarbase.mbc.nctu.edu.tw/) on the basis of minimum free energy (MFE) score. Further, different biological function related to PD for all target genes was explored using UniProt (http://www.uniprot.org/) database. Thereafter, basing on availability of MFE scores, seven PD associated target genes known to be regulated by nine miRNAs were considered for further study [5, 13].

Building protein-protein network

The protein-protein interaction network of miRNA target genes in PD was built using STRING (http://string-db.org/) web server. STRING builds networks for multiple proteins based on knowledge of text mining, experiments, co-expression, gene neighbourhood, gene fusion, co-occurrence and databases [15].

Multiple sequence alignment

Multiple sequence alignment (MSA) between selected miRNAs reported in case of PD was performed using Clustal Omega (www.ebi.ac.uk/Tools/msa/clustalo/) of EMBL-EBI web server to study the sequence wide pattern conservation among them. Similarly, MSA was also performed between miRNAs target genes associated in PD pathology.

Study of binding affinity between miRNAs and their target genes

A computational approach was carried out to verify the folding affinity between selected miRNAs and their target genes. Secondary structures miRNAs-mRNA duplexes were

predicted using RNAfold (http://rna.tbi.univie.ac.at/cgi-bin/RNAfold.cgi) web server. The resulted dot bracketed structures of duplex were used for prediction of their tertiary structure using RNA COMPOSER (http://rnacomposer.cs.put.poznan.pl/) tool [5, 13].

Retrieval and structure correction of AGO protein

The three-dimensional structure of AGO protein was retrieved from Protein Data Bank (PDB ID: 3F73). The structure preparation and correction were performed using Discovery Studio 3.5 suite (http://accelrys.com/products/discovery-studio/visualization-download.php).

Molecular docking

Molecular docking is an *in silico* method to predict the binding affinity and molecular interaction between protein and ligand which may be a small chemical compound [11] or between protein and a biomolecule like miRNA or mRNA [5, 13]. Docking study was performed between AGO protein and miRNAs-mRNA duplexes such as miR-27b and CYP1B1, miR-124-3p and CYP1B1, miR-29a and CDC42 using Patch Dock (https://bioinfo3d.cs.tau.ac.il/PatchDock/) web server [13]. The PatchDock algorithm generally ranks the dock complexes on the basis of highest geometrical shape complementary scores. The molecular interaction between docked complexes was studied and presented using Discovery Studio 3.5 suite.

Results and discussion

Building strategy for selection of PD associated miRNAs and their targets

miRNAs play a vital role in many developmental process and stress responses in both animal and plant [17]. Therefore, literature search was carried out to understand miRNAs based gene regulation in PD related genes. Total thirty one miRNAs and twenty three target genes such as LRRK2, SNCA, GBA, FGF20, PitX3, BDNF, CYP1B1, GCH1, CYP1A1, Pax6, Ptc-1, DJ-1, Parkin, CDC42, IGF-1, E2F1, Nurr1, ACHE, CX3CL1, FGFR1, L1CAM, SPTAN1, and DP (Table 1) reported to be involved in PD pathophysiology [9, 2-4, 7, 8, 10, 12, 16] were selected for study. miRTarbase web server was used to inspect the binding affinity between miRNAs-mRNA duplexes. The resulted miRNAs target sites and their binding affinity towards mRNAs in form of MFE scores were mentioned in Table 1. As of the availability of MFE scores, six miRNAs (miR-205-5p, miR-1-3p, miR-27b, miR-124-3p, miR-125b-5p, miR-29a) and seven target genes were selected (Table 1). Further, participation of seven target genes in biological activity related to different neurological disease and in particular PD such as aggresome assembly, epoxygenase P450 pathway, regulation of neuron apoptotic process, neurogenesis, nervous system development, angiogenesis, and other functions were investigated and reported using UniProt web server (Table 2). Among seven target genes, it was observed CYP1B1 regulates mostly epoxygenase P450 pathway, neuronal apoptotic, angiogenesis process. Similarly, it was noticed CDC42 gene involves in regulation of neuronal apoptotic, neurogenesis, and angiogenesis process (Fig. 1). Further, protein-protein network among those seven genes (LRRK2, BDNF, CYP1B1, GCH1, CYP1A1, CDC42, and IGF1) using STRING [15] algorithm was established that four genes such as LRRK2, CDC42, BDNF, and IGF1 have strong functional association while GCH1 was found as an isolated node in the network (Fig. 2A). Furthermore, it was noticed few genes such as BDNF, GCH1, IGF1 and CDC42, IGF1 associated with PD pathophysiology are regulated by two important miRNAs such as miR-1-3p and miR-29a respectively (Fig. 2B). The sequence level conservation pattern of six miRNAs (Fig. 3B) and seven target genes (Fig. 3A) were studied and reported. Additionally, strong binding affinity was established through good MFE score and predicted binding energy score between miRNAs-mRNA duplexes such as CYP1B1-miR-27b, CYP1B1-miR-124-3p, and CDC42-miR-29a (Table 3).

Table 1. Thirty one miRNAs and twenty three target genes associated with Parkinson's disease

No	Gene	miRNA	Position	Expression	MFE Score	Reference
1	**LRRK2**	**miR-205-5p**	**103 - 123**	**down**	**-17.90**	**[8, 9]**
		miR-184		down	NA	
		miR-1224		down	NA	
		miR-1224		down	NA	
2	SNCA	miR-7		down	NA	[2, 7-9, 16]
		miR-153		down	NA	
3	GBA	miR-127-5p		down	NA	[9]
		miR-16-5p		down	NA	
4	FGF20	miR-433		up	NA	[2, 4, 7, 16]
5	PitX3	miR-133b		down	NA	[2, 7, 16]
6	**BDNF**	**miR-1-3p**	**1305 - 1328**	**up**	**-14.80**	**[16]**
7	**CYP1B1**	**miR-27b**	**2726 - 2750**	**up**	**-26.70**	**[16]**
		miR-124-3p	**3006 - 3025**	**up**	**-14.00**	**[16]**
8	**GCH1**	**miR-1-3p**	**60 - 83**	**up**	**-12.20**	**[16]**
		miR-133b		up	NA	[16]
9	**CYP1A1**	**miR-125b-5p**	**273 - 297**	**up**	**-14.60**	**[16]**
10	Pax6	miR-7a-5p		down	NA	[16]
11	Ptc1	miR-64		up	NA	[16]
		miR-65		up	NA	[16]
12	DJ1	miR-34b		down	NA	[2, 8]
		miR-34c		down	NA	
13	Parkin	miR-34b		down	NA	[2, 8]
		miR-34c		down	NA	
		miR-181a		down	NA	
		miR-181b		down	NA	
		miR-181c		down	NA	
		miR-181d		down	NA	
14	**CDC42**	**miR-29a**	**983 - 1004**	**NA**	**-18.70**	**[4]**
15	**IGF1**	miR-30		down	NA	**[10]**
		miR-29a	**917 - 942**	**down**	**-17.10**	
		miR-1-3p	**171 - 192**	**down**	**-10.49**	
16	E2176F1	miR-184		up	NA	[7, 12]
		Let-7a-5p		up	NA	
17	Nurr1	miR-132		down	NA	[8]
18	ACHE	miR-29a		up	NA	[3]
19	CX3CL1	miR-132		down	NA	[3]
20	FGFR1	miR-133a-1		NA	NA	[3]
21	L1CAM	miR-182		NA	NA	[3]
22	SPTAN1	miR-330		NA	NA	[3]
23	DP	miR-184		NA	NA	[3]
		Let-7		up	NA	[7]

NA: Not available; MFE: Minimum free energy

Table 2. Seven target genes involved in different biological function are reported from UniProt (http://www.uniprot.org/) web server. Two genes highlighted in bold have maximum involvement in different biological activity related to Parkinson's disease.

Gene	**Function**						
	Aggresome assembly	Epoxygenase P450 pathway	Regulation of neuronal apoptotic process	Neurogenesis	Nervous system development	Angiogenesis	Other function
LRRK2	1		2				3
BDNF			1		2		3
CYP1B1		1	2			3	4
GCH1							1
CYP1A1		1					2
CDC42			1	2		3	4
IGF1	1		2				3

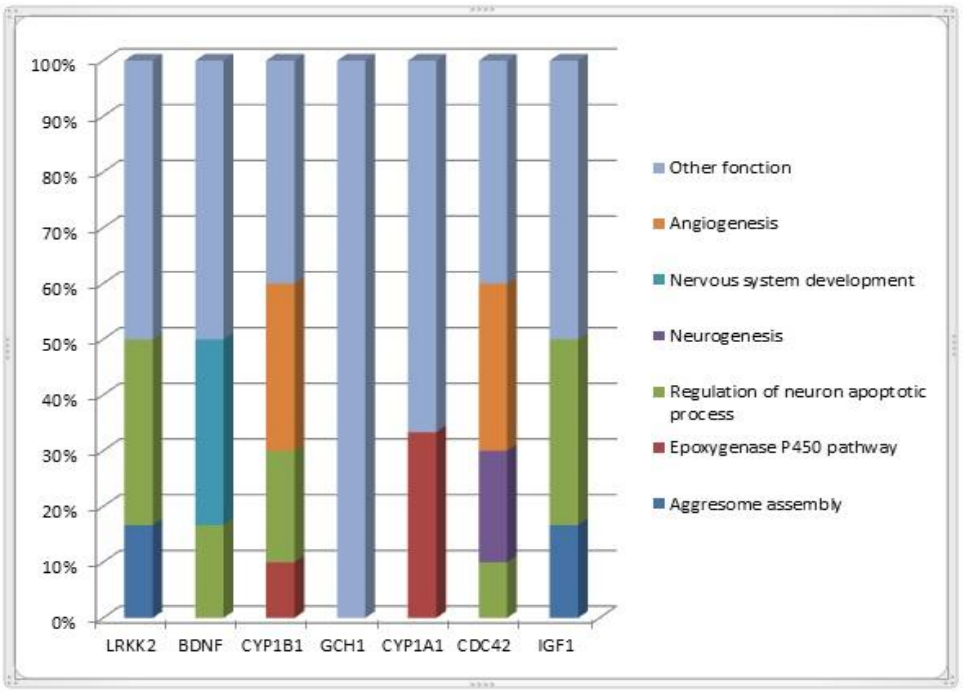


Fig. 1 Involvement of seven target genes in different biological functions like angiogenesis, apoptosis, aggresome assembly, epoxygenase P450 pathway, neurogenesis, nervous system development and others are plotted. Different colour represents involvement of each gene in different biological functions.

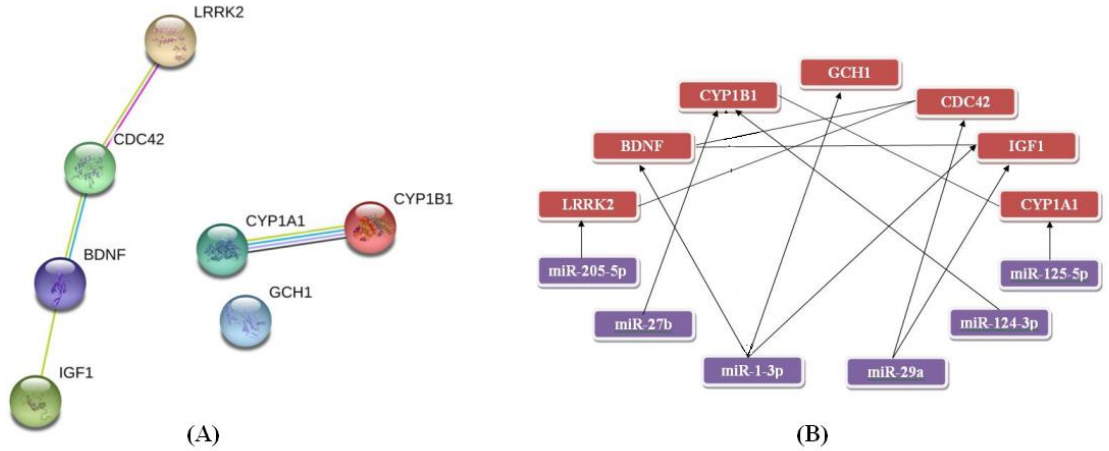


Fig. 2 Functionality based protein-protein network resulted using STRING and schematic diagram of miRNAs based gene regulation for seven target genes are represented in section (A), and (B), respectively. In the section (B), the protein-protein association presented using straight line where as arrow is used to present miRNAs regulating genes.

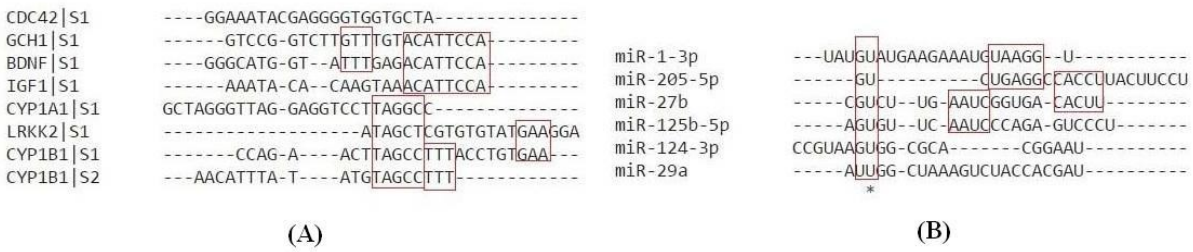
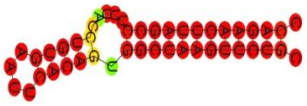


Fig. 3 The similarity between sequences of seven mRNAs and six miRNAs were inspected and deciphered separately in section (A) and (B) respectively.
The conserve sequence patterns are highlighted in red box.

Table 3. Secondary folding pattern between miRNAs-mRNA target genes, predicted binding energy and MFE scores obtained from miRTarbase web server

No	Gene	miRNAs	Dot-bracket image	Secondary structure of miRNA-mRNA duplex	Binding energy (kcal/ mol)	MFE Score (kcal/ mol)
1	CYP1B1	miR-27b	((((((((((((.....(((((....))))).)))))))))))).		-23.50 kcal/mol	-26.70
		miR-124-3p	(((((((.(((.((((....)))))))..)))))))..		-11.60 kcal/mol	-14.00
2	CDC42	miR-29a	(((.(((((((((....)))))))))....)))....		-14.70 kcal/mo	-18.70

MFE: Minimum free energy

CYP1B1 (Cytochrome P450 1B1) is a member of Cytochrome P450 super family which is considered as one of the first line defence against toxicity produced through drugs, environmental chemicals, and thereby detoxification of toxins by cerebral CYP1B1 might be crucial [14]. On the other hand, human CDC42 is a small GTPase of the Rho family, a key regulating enzyme that controls diverse cellular function including cell morphology, migration, endocytosis and cell cycle progression. CDC42-mediated microglial mobility is affected due to intoxication of dopaminergic neurons and induces gliapses (body-to-body neuron-glia contacts) and may lead to PD pathology [1]. In this connection molecular docking was planned to study the binding affinity between CYP1B1-miR-27b, CYP1B1-miR-124-3p, and CDC42-miR-29a and with AGO protein. Molecular docking between protein and miRNA or between protein and miRNA-mRNA complex is an efficient computational procedure to inspect molecular interaction at atomic level [5, 13].

The 3.0 Å crystal structure AGO protein (PDB ID: 3F73) contains two chains with 685 amino acid length. The AGO protein was prepared by removing all water molecules, guide DNA and target RNA duplexes present in the structure. Out of two chains, only chain 'A' of AGO protein was considered and refined before docking. The necessary correction in bond order and bond length of all atoms in the structure was performed using prepare protein and clean geometry protocol of Discovery studio 3.5 suite. As miRNAs needs the assistance of AGO class of protein to bind with the target genes, therefore independent molecular docking was performed between AGO and selected three miRNAs such as miR-27b, miR-124-3p, and miR-29a using PatchDock algorithm [13]. The predicted atomic contact energy between AGO and miR-27b found as quite good in comparison to rest two miRNAs suggested for a strong affinity (Table 4). Further, to study the atomic interaction the amino acid residues of AGO protein interacting with miR-27b, miR-124-3p, and miR-29a within a distance of 3.5 Å were inspected and reported (Table 5, Fig. 4). Few amino acids are commonly found during molecular interaction such as ILE 173, LEU 279, ALA 414, ILE 434, ALA 644, ALA 648, VAL 685 in hydrogen bonding (Fig. 5) TYR 171, PHE 649 as aromatic ring, and TYR 171, LEU 279, MET 413, GLN 433, ALA 648 identified as hydrophobic in nature within the binding cavity of AGO protein (Table 5). Inter atomic distances of amino acids of AGO protein participated in hydrogen bonding within a distance of 2.5 Å with miRNAs (miR-27b, miR-124-3p, and miR-29a) are calculated and reported in Table 6, supported for a strong binding between AGO and miRNAs at atomic level. The predicted three dimensional binding modes of the CYP1B1 with miR-27b, CYP1B1 with miR-124-3p, and CDC42 with miR-29a established as a proof of energetically favourable interaction between them (Fig. 6). Finally, molecular interaction between the AGO protein and miRNAs-mRNA duplexes (CYP1B1-miR-27b, CYP1B1-miR-124-3p, CDC42-miR-29a) were studied through molecular docking using PatchDock algorithm [13]. PatchDock algorithm produces ten docked complexes for each independent docking and the highest-scoring complex is generally considered as best binding mode.

Table 4. Docking score between miRNAs and AGO (PDB ID: 3F73, Chain A) protein

miRNA	**Score**	**Area**	**ACE**
miR-27b	17412	2353.90	-242.63
miR-124-3p	17148	2236.90	-34.53
miR-29a	17202	2263.20	-69.32

ACE: Atomic contact energy

Table 5. Amino acid residues of AGO protein interacting with miR-27b, miR-124-3p, and miR-29a within a distance of 3.5 Å

miRNA	**Amino acid residues**		
	Hydrophobic interaction[a]	**With aromatic ring[b]**	**Hydrogen bonding[c]**
miR-27b	**ILE 173**, ILE 254, **LEU 279**, LEU 281, **ALA 414**, **ILE 434**, VAL 606, **ALA 644**, **ALA 648**, **VAL 685**	**TYR 171**, TRP 202, TYR 642, **PHE 649**	ARG 81, **TYR 171**, ARG 200, LYS 252, ARG 286, **LEU 279**, **MET 413**, **GLN 433**, ILE 434, ASN 436, ARG 548, VAL 549, PRO 550, ARG 580, THR 613, TYR 642, **ALA 648**, PHE 649, HIS 657, ARG 661, VAL 685
miR-124-3p	**ILE 173**, LEU 267, **LEU 279**, **ALA 414**, **ILE 434**, LEU 439, **ALA 644**, **ALA 648**, **VAL 685**	**TYR 171**, PHE 360, TRP 415, **PHE 649**	**TYR 171**, PRO247, PRO 250, THR 266, **LEU 279**, **MET 413**, ARG 418, **GLN 433**, ARG 440, GLU 442, ASN 449, ALA 644, SER 645, **ALA 648**, PHE 649, VAL 685
miR-29a	**ILE 173**, LEU 265, LEU 267, **LEU 279**, LEU 281, **ALA 414**, **ILE 434**, LEU 435, ALA 450, VAL 606, **ALA 644**, **ALA 648**, **VAL 685**	**TYR 171**, TRP 415, **PHE 649**	**TYR 171**, LYS 191, ARG 192, GLU 203, LEU 265, THR 266, LEU 267, **LEU 279**, **MET 413,** **GLN 433**, GLY481, ARG 482, THR 613, ARG 615, **ALA 648**, PHE 649, ALA 644 ARG 651

[a]amino acid residues involved in hydrophobic interactions; [b]amino acid residues with aromatic rings; [c]amino acid residues participating in hydrogen bonding.
Commonly found amino acid residues represented in bold.

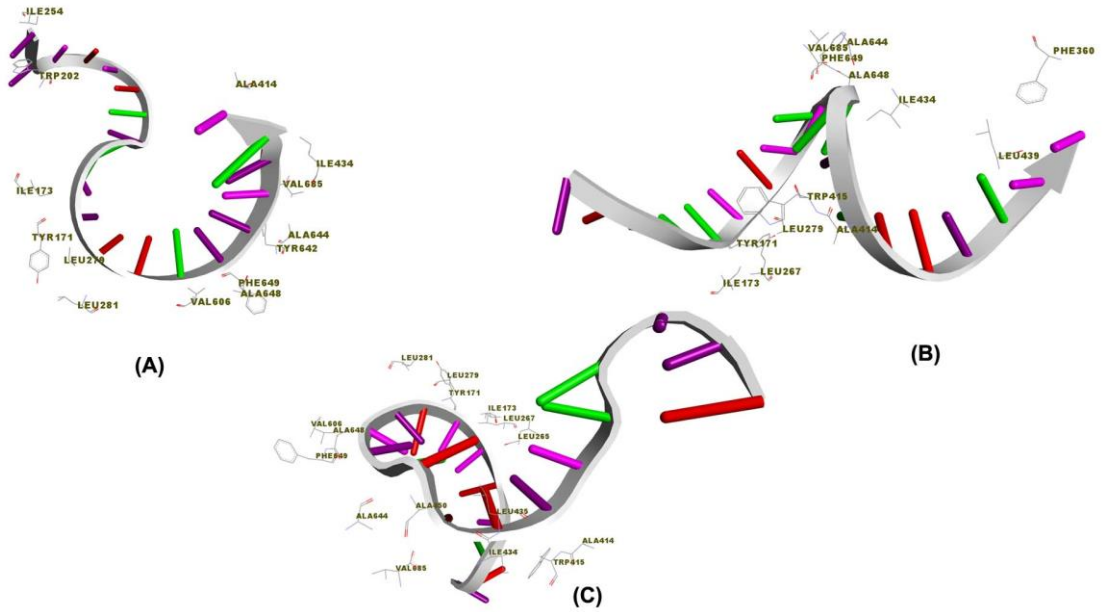


Fig. 4 Amino acid residues of AGO protein participating in interaction with:
A) miR-27b; B) miR-124-3p; and C) miR-29a within a distance of 3.5 Å, respectively.

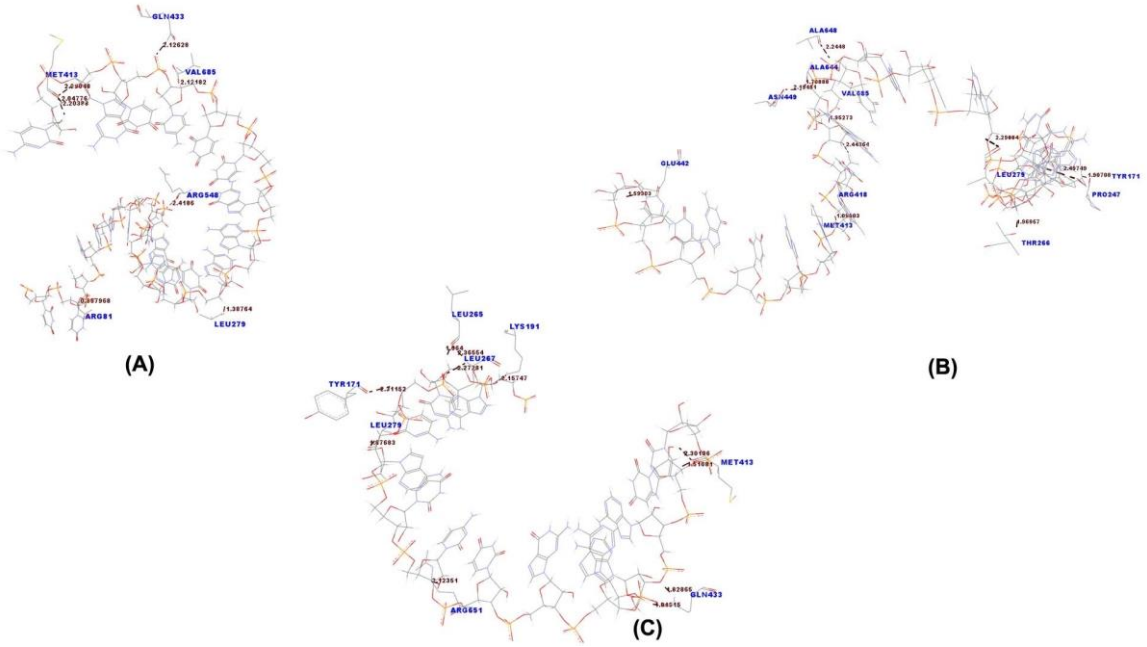


Fig. 5 Amino acid residues of AGO protein participating in polar interaction with: A) miR-27b; B) miR-124-3p; C) miR-29a within a distance of 2.5 Å, respectively.

Table 6. Amino acid residues of AGO protein participating in hydrogen bonding with miRNAs within a distance of 2.5 Å

miRNA	**Residues**	**Atom**	**Distance**
miR-27b	ARG 81	O…H5' (C28)	0.857
	LEU 279	O…H4' (A38)	1.387
	MET 413	O…H4'(G45)	2.290
	MET 413	O…HO3' (C46)	2.203
	MET 413	O…H4' (C46)	2.047
	GLN 433	NE2…OP1 (U44)	2.126
	ARG 548	O…H3' (U33)	2.418
	VAL 685	O…H4' (C43)	2.121
miR-124-3p	TYR 171	O…H4'(C26)	2.497
	PRO247	O…H2 (A22)	1.907
	THR 266	OG1…H5' (G25)	1.969
	LEU 279	O…H5'' (A27)	2.298
	MET 413	O…H5'' (G34)	1.093
	ARG 418	NH2…O2' (G32)	2.443
	GLU 442	OE2…H5' (C40)	1.593
	ASN 449	OD1…H5'' (G31)	2.194
	ALA 644	O…H5' (G31)	1.708
	ALA 648	O…H5'' (C30)	2.244
	VAL 685	OXT…H4'(G32)	1.952
miR-29a	TYR 171	O…H4' (C29)	2.311
	LYS 191	CE…O41 (A27)	2.157
	LEU 265	O…H5'' (C280	2.365
	LEU 265	O…H4' (C28)	1.663
	LEU 267	N…OP1 (C29)	2.272
	LEU 279	O…H5''(A30)	1.876
	MET 413	O…HO2'(U38)	2.301

MET 413	O…H4' 9U38)	1.510
GLN 433	OE1…H4' (A36)	1.815
GLN 433	NE2…O3'(A36)	1.828
ARG 651	CD…O2' (C32)	2.123

Commonly found amino acid residues represented in bold.

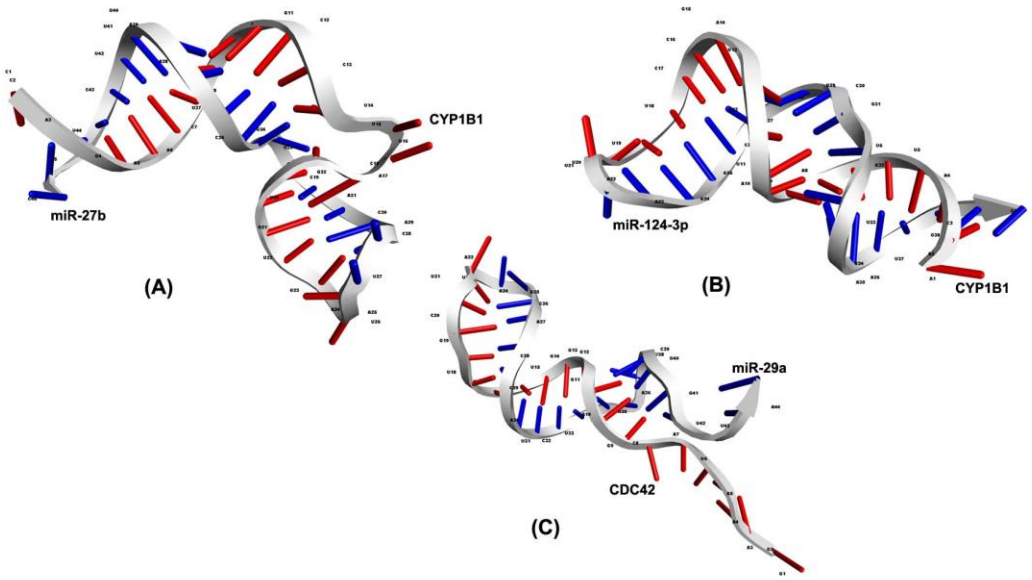


Fig. 6 Energetically stable tertiary binding modes of:
A) miR-27b and mRNA of CYP1B1 gene;
B) miR-124-3p and mRNA of CYP1B1 gene;
C) miR-29a and mRNA of CDC42 gene, respectively.

However, a good docking score in all cases of docking between the selected miRNAs and AGO protein implicated a strong interaction between them at molecular level (Table 7). Amino acid residues participated during interaction with miRNAs within the binding cavity of AGO protein were reported in Table 8. Generally strong hydrophobic amino acids and amino acids with aromatic ring structure which are relatively hydrophobic in nature are contributing towards hydrophobic interaction and considered as a positive addition towards the stability in the binding moiety during interaction. The presence of hydrophobic amino acids and amino acids with aromatic rings (Table 8, Fig. 7) during the molecular interaction between AGO and miRNAs-mRNA (CYP1B1-miR-27b, CYP1B1-miR-124-3p, CDC42-miR-29a) duplexes, confirmed their strong binding affinity at atomic level.

Table 7. Docking score between miRNAs-mRNA duplex and AGO (PDB ID: 3F73, Chain A) protein

miRNAs-mRNA duplex	Score	Area	ACE
miR-27b- CYP1B1	20508	3593.40	-520.84
miR-124-3p-CYP1B1	20326	3232.00	-525.91
miR-29a-CDC42	23194	3576.00	-48.94

Table 8. Amino acid residues of AGO protein participating in the interaction with miR-27b and CYP1B1, miR-124-3p and CYP1B1 and miR-29a and CDC42 within a distance of 3.5 Å

miRNA-mRNA duplex	**Amino acid residues**	
	Hydrophobic interaction[a]	**With aromatic rings[b]**
miR-27b and CYP1B1	VAL 58, VAL 108, ALA 111, VAL 157, LEU 204, LEU 205, ILE 434, LEU 435, VAL 437, VAL 549	TYR 43, TRP 156, **TRP 415**, TRP 447, PHE 487
miR-124-3p and CYP1B1	VAL 42, ALA 47, VAL 58, ALA 111, LEU 132, ALA 133, VAL 152, VAL 264, LEU 267, LEU 270, LEU 277, LEU 435, ALA 450, VAL573, ALA 644, LEU 652	TYR 43, TYR 135, **TRP 415**, ILE 434,
miR-29a and CDC42	LEU 132, ALA 133, VAL 152, LEU 265, LEU 267, LEU 277, ALA 278, LEU 279, ALA 479, VAL 549, VAL 663, VAL 685	TYR 86, **TRP 415**

[a]amino acid residues involved in hydrophobic interactions; [b]amino acid residues with aromatic rings. The amino acid residues of AGO protein commonly participated in more than one miRNA-mRNA duplex represented in bold.

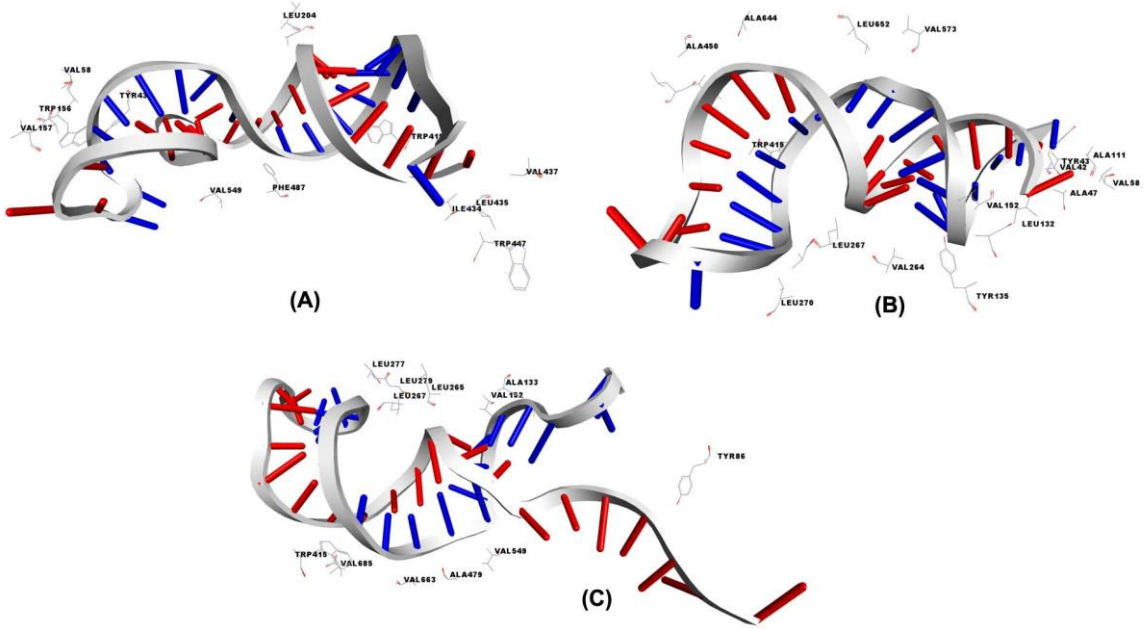


Fig. 7 Amino acid residues of Argonaute (AGO) protein participating in interaction with:
A) duplex of miR-27b and mRNA of CYP1B1 gene;
B) miR-124-3p and mRNA of CYP1B1 gene and miR-29a;
C) mRNA of CDC42 gene within a distance of 3.5 Å, respectively.

Conclusion

miRNAs profiling studies have crucial role to understand disease pathophysiology of neurological disorders, in particular PD. Selection of miRNAs and their target genes associated with PD pathology were investigated through different strategy to understand the molecular mechanism behind miRNAs based gene regulation.

We found the interaction between three important miRNAs, such as miR-27b, miR-124-3p up regulating CYP1B1 gene and mir-29a regulating the expression of CDC42 gene by implicating *in silico* approach. The molecular docking study supported for high binding affinity with energetically favourable state between miRNAs-mRNA (miR-27b-CYP1B1, miR-124-3p-CYP1B1, CDC42-miR29a) duplexes as well as between AGO protein and miRNAs-mRNA (miR-27b-CYP1B1, miR-124-3p-CYP1B1, CDC42-miR29a) complexes at atomic level. The present findings may throw light upon miRNAs based gene regulation in PD.

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Assist. Prof. Surya Narayan Rath
E-mail: snrbioinfo@gmail.com

Surya Narayan Rath is working as Assistant Professor and Co-PI of DBT-BIF Centre in the Department of Bioinformatics, Centre for Post Graduate Studies, Odisha University of Agriculture & Technology, Bhubaneswar, Odisha, India. Mr. Rath has ten years of teaching and research experience in the field of Bioinformatics. He is continuing his Ph.D. in Neurobiology Laboratory, Department of Zoology, School of Life Sciences, Ravenshaw University, Cuttack, Odisha, India. To his credit, he has published fifteen research papers in journals of international repute. His area of interest is neuroinformatics, computational genomics, system biology, *in silico* drug design, and NGS data analysis. He has guided twenty students of M.Sc. Bioinformatics.

Assist. Prof. Manorama Patri, Ph.D.
E-mail: mpatri@ravenshawuniversity.ac.in

Dr. Manorama Patri is working as Assistant Professor, Neurobiology Laboratory, Department of Zoology, School of Life Sciences, Ravenshaw University, Cuttack, Odisha, India. Dr. Patri has 17 years of teaching and research experience in undergraduate as well as postgraduate level and her published work deals with the cellular and molecular mechanism of glutamate receptors (e.g. NMDA receptor) involved in the learning and memory as well as anxiety-like behavior in Wistar rats during postnatal brain development. She has published 21 research papers in different peer reviewed journals and she is the PI of research funding from DAE-BRNS, Mumbai, DST, Odisha and DRDO, New Delhi.