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# The features of novel miRNAs interaction with mRNA candidate genes having trinucleotide repeats in coding sequences and untranslated regions

**Abstract.** Trinucleotide repeat disorders are a group of predominantly inherited neurological diseases caused by the expansion of repetitive sequences. miRNAs play major roles in transcriptional regulation and are expressed selectively and abundantly in the central nervous system. In the present research, MirTarget program predicted the miRNA-binding sites in mRNAs of genes with trinucleotide repeats. The MirTarget programme determines the following features of binding: the start of the initiation of miRNA binding to mRNAs; the localization of miRNA binding sites in 5'UTRs, CDSs and 3'UTRs; the free energy of binding; and the schemes of nucleotide interactions between miRNAs and mRNAs. In coding sequences the binding sites of ID00372.5p-miR with mRNA of *ATXN2, FMN2* and *MN1* genes having CAG (Q) repeats show the highest free binding energy**.** The mRNA of *ADRBK1, BRSK2, C11orf87* and *FMR1* genes have ID01508.5p-miR binding sites in 5'UTR with CGG repeated regions. Also, the binding sites of ID00296.3p-miR and ID01702.3p-miR in 5'UTR of *BLMH* gene interacted with CCG repeats. *DMPK* gene with CUG repeated regions have ID00522.5p-miR binding sites in 3'UTR. Based on these results, the interactions of ID00372.5p-miR, ID01508.5p-miR, ID00296.3p-miR, ID01702.3p-miR and ID00522.5p-miR and their target genes *ATXN2, FMN2, MN1, ADRBK1, BRSK2, C11orf87, FMR1, BLMH* and *DMPK* can be used for developing methods for diagnosing and therapeutic targets for neurological disorders.
**Key words:** miRNA, mRNA, binding site, coding sequence, untranslated regions, trinucleotide repeat.

## Introduction

The extension of a tandem repeat array is responsible for disease pathology in a community of genetic disorders, repeat extension diseases including, Fragile-X syndrome (FXS) [1], amyotrophic lateral sclerosis (ALS) [2], Alzheimer's disease (AD) [3], Intellectual disability (ID) [4], Schizophrenia [5], Huntington disease [6] and neuromuscular and myotendinous junctions [7].The critical point in the development of new therapeutic strategies for neurological disorders (NDs) is identifying the role of miRNAs in normal cellular processes and understanding how dysregulated miRNA expression is responsible for their neurological effects, also dysregulation of miRNA has been implicated in different NDs [8]. miRNAs are group of 22-nucleotide short RNA sequences, which mediate the post-transcriptional gene silencing [9]. In neurological disorders, regulating the expression and processing of miRNAs, and the mechanisms by which miRNAs locate to their correct targets, is not yet fully understood [10]. The first researches of target prediction algorithms performance was carried out by TargetScanS, PicTar, DIANA-microT and EIMMO. TargetScanS, PicTar and miRanda used alone or as a union made the best trade off between sensitivity and specificity while TargetScan and DIANA-microT did not succeed [11]. Therefore in this study, using MirTarget program, we predicted the features of the interaction of miRNAs from a wide list of Londin *et al.* (Londin, 2015: 1106) with mRNA of candidate genes with trinucleotide repeats in coding sequences (CDS) and untranslated regions (UTRs).

## Materials and methods

The nucleotide (nt) sequences of candidate genes of having trinucleotide repeats were downloaded from GenBank (http://www.ncbi.nlm.nih.

gov). The nucleotide sequences of human novel miRNAs were taken from Londin *et al.* (Londin, 2015: 1106) [12].The search for miRNA target genes were carried out using the MirTarget program, which was developed in our laboratory. The MirTarget program defines the following characteristics of miRNA binding to mRNAs: (a) the commencement of miRNA binding to mRNA; (b) the localization of miRNA binding sites in 5'UTRs, CDSs and 3'UTRs of the mRNAs; (c) the free energy of interaction between miRNA and the mRNA (ΔG, kJ/mole); and (d) the schemes of nucleotide interactions between miRNAs and mRNAs. This program found hydrogen bonds between adenine (A) and uracil (U), guanine (G) and cytosine (C), G and U, and A and C. The ratio ΔG/ΔGm (%) was counted for each site,where ΔGm equaled the free energy of a miRNA binding with its perfect complementary nucleotide sequence [13].

**Results and discussion**

A study of 3701 novel miRNAs binding to mRNAs of 371 genes of having nucleotide repeats showed that 41 genes were targets for seven miRNAs in CDS with CAG trinucleotide repeats. Also, in untranslated regions (5/3'UTRs) 52 miRNAs bind with 25 mRNA genes having CGG, CCG and CUG trinucleotide repeats with ΔG/ΔGm values equal to 85 % and more.

The binding sites of ID00372.5p-miR, ID03311.5p-miR, ID01508.5p-miR, ID00296.3p-miR, ID01702.3p-miR, ID00930.3p-miR, ID02986.5p-miR, ID00457.3p-miR and ID00522.5p-miR in mRNA of 59genes have the highest free binding energy from -101 kJ/mole to -123 kJ/mole in CDS with CAG trinucleotide repeat, and between -104 kJ/mole to -148 kJ/mole in 5'UTRand 3'UTR with CGG,CCG,CUG repeats withΔG/ΔGm value from 85% to 98%, respectively.

Table 1 shows that ID00372.5p-miR, ID03311.5p-miR, ID01508.5p-miR, ID00296.3p-miR and ID01702.3p-miR bind three or more mRNA genes. However in the CUG repeat region ID00930.3p-miR, ID02986.5p-miR, ID00457.3p-miR and ID00522.5p-miR bind only one gene mRNA. Moreover, 20 genes are targets of two or more miRNAs. For example, we can see that the mRNA of *ATXN1, ATXN2, ELMSAN1, FBXO11, FMN2, GIGYF2, IRS1, MED15, MEF2A* and *MN1* genes are targets for ID00372.5p-miR and ID03311.5p-miR in CDS. ID00296.3p-miR, ID01702.3p-miR, ID02986.5p-miR and ID00522.5p-miR can bind to the mRNAs of *AFF2, ANKH, ANKRD13D, BCL11A, BCL2L11, BLMH, BTF3L4, C4orf19*, *CA10* and *DMPK* genes in 5'UTR and 3'UTR.

**Table 1 –** The list of miRNAs binding sites in mRNA of two or more genes having trinucleotide repeats

| miRNA | Gene | Region mRNA |
|---|---|---|
| ID00372.5p-miR | *ATXN1, ATXN2, ELMSAN1, FBXO11, FMN2, GIGYF2, IRS1 MED15, MEF2A, MN1* | CDS |
| ID03311.5p-miR | *AR, ATN1, ATXN1, ATXN2, ATXN7, CELF3, DACH1, DCP1B, DENND4B, DLX6, DNER, E2F4, EGR1, ELMSAN1, EP400, ERN1, FAM104A, FAM155A, FAM157A, FAM157B, FBXO11, FMN2, FOXJ2, FOXP2, FRMPD3, GIGYF2, HTT, IRS1, MAML3, MED15, MEF2A, MLL2, MN1, NCOR2, RUNX2, SMARCA2, TBP, TNRC6B, TOX3, ZNF384* | CDS |
| ID01508.5p-miR | *ADRBK1, B4GALT2, BRSK2, C11orf87, CARM1, CBL, CCDC93, FMR1* | 5'UTR |
| ID00296.3p-miR | *AFF2, ANKH, ANKRD13D, BCL11A, BCL2L11, BLMH, BTF3L4, C4orf19, CA10* | 5'UTR |
| ID01702.3p-miR | *ABCD3, AFF2, ANKH, ANKRD13D, BCL11A, BCL2L11, BLMH, BTF3L4, C4orf19, CA10* | 5'UTR |
| ID00930.3p-miR | *ATP6V0B* | 3'UTR |
| ID02986.5p-miR | *DMPK* | 3'UTR |
| ID00457.3p-miR | C15orf39 | 3'UTR |
| ID00522.5p-miR | DMPK | 3'UTR |

From these binding sites, the mRNA genes of *ATXN2, ,FMN2, IRS1, MN1, ADRBK1, B4GALT2, BRSK2, C11orf87, CARM1, CBL, CCDC93* and *FMR1* have binding sites for ID00372.5p-miR and ID01508.5p-miR with the highest free binding energy equal to -121 and -123 kJ/mole in CDS with CAG, and 5'UTR with CGG repeated regions. Also, the binding sites of ID00296.3p-miR and ID01702.3p-miR with 5'UTR mRNA of *BLMH* and *C4orf19* genes having CCG repeats show the

highest free binding energy equal to -148 kJ/mole. The mRNA of *ATP6V0B, C15orf39* and *DMPK* genes with free binding energy from -118kJ/mole to -123kJ/mole have ID00930.3p-miR, ID00457.3p-miR and ID00522.5p-miR binding sites in 3'UTR with CUG repeated regions (Table 2).

**Table 2 –** The characteristics of miRNAs interaction with mRNA of having trinucleotide repeat genes with the highest free binding energy

| miRNA | Gene | Start of site, nt | Region mRNA | ΔG, kJ/mole) | ΔG/ ΔGm,% | Length miRNA,nt | Nucleotide repeat |
|---|---|---|---|---|---|---|---|
| ID00372.5p-miR | *ATXN2* | 654 | CDS | -121 | 89 | 24 | CAG |
| | *FMN2* | 836 | CDS | -123 | 90 | 24 | CAG |
| | *IRS1* | 2085 | CDS | -121 | 89 | 24 | CAG |
| | *MN1* | 1861 | CDS | -121 | 89 | 24 | CAG |
| ID01508.5p-miR | *ADRBK1* | 220 | 5'UTR | -123 | 85 | 23 | CGG |
| | *B4GALT2* | 137 | 5'UTR | -123 | 85 | 23 | CGG |
| | *BRSK2* | 103 | 5'UTR | -123 | 85 | 23 | CGG |
| | *C11orf87* | 17 | 5'UTR | -123 | 85 | 23 | CGG |
| | *CARM1* | 15 | 5'UTR | -123 | 85 | 23 | CGG |
| | *CBL* | 15 | 5'UTR | -123 | 85 | 23 | CGG |
| | *CCDC93* | 33 | 5'UTR | -123 | 85 | 23 | CGG |
| | *FMR1* | 101 | 5'UTR | -123 | 85 | 23 | CGG |
| ID00296.3p-miR | *BLMH* | 184 | 5'UTR | -148 | 94 | 25 | CCG |
| | *C4orf19* | 75 | 5'UTR | -148 | 94 | 25 | CCG |
| ID01702.3p-miR | *BLMH* | 184 | 5'UTR | -148 | 98 | 24 | CCG |
| | *C4orf19* | 75 | 5'UTR | -148 | 98 | 24 | CCG |
| ID00930.3p-miR | *ATP6V0B* | 901 | 3'UTR | -118 | 86 | 22 | CUG |
| ID00457.3p-miR | *C15orf39* | 4049 | 3'UTR | -118 | 87 | 22 | CUG |
| ID00522.5p-miR | *DMPK* | 2310 | 3'UTR | -123 | 87 | 23 | CUG |

From indicated in table 2 genes, especially *ATXN2, FMN2, MN1, ADRBK1, BRSK2, C11orf87, FMR1, BLMH* and *DMPK* genes are the major responsible causes forneurological disorders (Table 3). These genes are targets for ID00372.5p-miR, ID01508.5p-miR, ID00296.3p-miR, ID01702.3p-miR and ID00522.5p-miR. Moreover, below we discuss miRNAs binding sites with these genes and their functions in neurodevelopmental disorders (Table 3).

In CDS the mRNA of *ATXN2* gene has $(CAG)_{22}$ repeat between 658 to 726. Usually larger than 34 repeat CAG expansions in coding regions of the *ATXN2* gene are the cause of type 2 spinocerebellar ataxia (SCA2) [14]. Also, CAG repeats in the *ATXN2* gene were linked to an increased risk of amyotrophic lateral sclerosis (ALS) [15]. ID00372.5p-miR binding sites located from 654 nt to 677 nt, encodes polyQ with an interaction value ΔG/ΔGm of 89%.

The binding sites of ID00372.5p-miR in mRNA of *FMN2* and *MN1* genes have $(CAG)_6$ trinucleotide repeats of which binding sites started in 836 and 1861 nt in the CDS (Figure 1). *FMN2* was associated with synapse formation and deletion mutations are associated with intellectual disability, suggesting a role for *FMN2* in memory function in mice and humans [16; 17]. Also, recently research studies shows that *FMN2* was highly expressed in human hippocampal neurons and the mouse [18]. For patients with post-traumatic stress disorder (PTSD) and Alzheimer's disease (AD), *FMN2* is deregulated [18]. *MN1* gene, located on human chromosome 22, was first cloned in 1995 from a patient with t(4;22) (p16;q11) translocation meningioma, which in its first exon disrupts *MN1* [19]. *MN1* C-Terminal Truncation (MCTT) syndrome is a genetic disorder caused by an *MN1* gene alteration. A genetic modification of the *MN1* gene was related to intellectual disability (ID) [20].

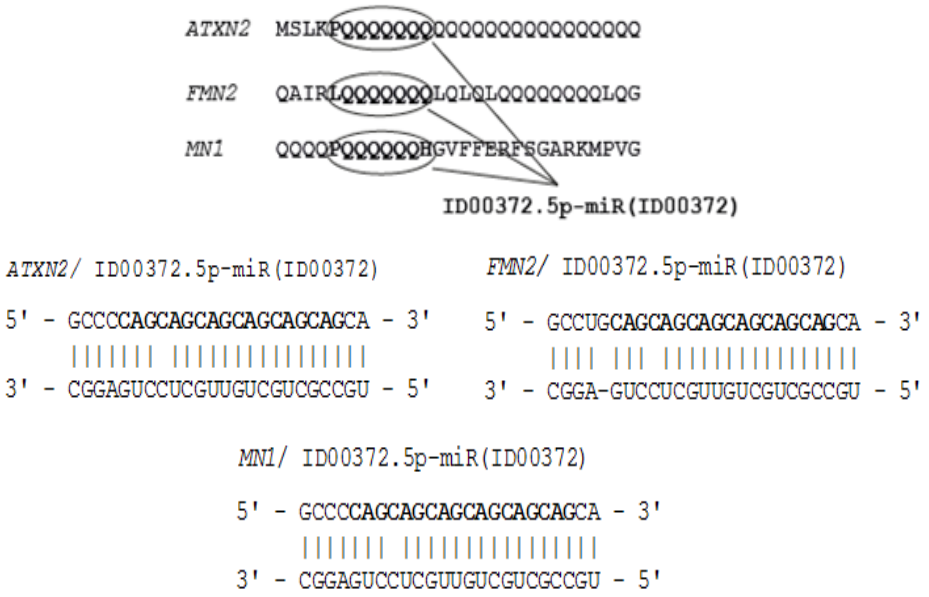


**Figure 1 –** The encoded oligopeptides and schemes of ID00372.5p-miR(ID00372) binding sites in CDS mRNA of *ATXN2, FMN2* and *MN1* genes

It can be seen from the figure 2 that the mRNA of four genes (*ADRBK1, BRSK2, C11orf87, FMR1*) are targets for ID01508.5p-miR in $(CGG)_8$ repeated regions in 5'UTR. It is known that these genes are responsible for the development of a number of neurodegenerative diseases.

Androgenic, beta, receptor kinase 1 *(ADRBK1)*, also known as *βARK, BARK*, or G-protein – coupled receptor kinase 2 (*GRK2*), produced serine / threonine intracellular kinase, a ubiquitous cytosolic enzyme that specifically phosphorylated the activated form of the beta-adrenergic and related G-protein – coupled receptors (GPCRs) [21-22]. *ADRBK1* related illnesses include heart disease and Alzheimer's disease [23].

*BRSK2* interacts with many genes related to neurodevelopmental disorders including autism, tuberous sclerosis, developmental delay and intellectual disability [24].

The *C11orf87* is mainly found in brain tissue, also known as neuronal integral membrane protein 1 (NEURIM1). It is the only gene present within a locus known to harbour variations associated with schizophrenia in multiple genome-wide association studies in different populations, as well as association with self-reported educational achievement [25].

*FMR1*, located at Xq27.3, consists of 17 exons and measures approximately 38 kb [26]. CGG-repeat expansion in the 5′-untranslated region (5′UTR) of *FMR1*, inducing abnormal methylation of this region followed by transcriptional silencing, is the major recurrent mutagenic mechanism leading to the absence of FMRP. This regular expansion is thought to account for at least 99% of FXS cases [27]. Fragile-X syndrome (FXS) is the most widely recognised form of inherited intellectual disability (ID), and its neurodevelopmental phenotype often overlaps with autism spectrum disorder [28; 29].

Noticeably in Figure 3, ID00296.3p-miR and ID01702.3p-miR occupied the same binding site, starting from184 nt to 208 nt with $(CCG)_7$ repeats in 5'UTR mRNA of *BLMH* gene.

*BLMH* is involved in homocysteine metabolism and homocysteine constitutes a risk factor for Alzheimer's disease (AD). *BLMH* is important in cytoskeleton dynamics, preserves synaptic plasticity and can associate the inactivation of the *BLMH* gene with AD [30].

Other mRNA gene of *DMPK* was a target of ID00522.5p-miR, for example: ID00522.5p-miR was bound the gene mRNA of *DMPK* (between 2310 nt -2333 nt*)* with $(CUG)_5$ repeats in 3'UTR (Figure 4). A CUG repeat in *DMPK* is transcribed and is located in the 3- prime untranslated region (UTR) of an mRNA that is expressed in tissues affected by myotonic dystrophy [31]. Immunohistochemical staining revealed that *DMPK* is predominantly located at sites of human and rodent skeletal muscle neuromuscular and myotendinous junctions. The protein could also be seen in the neuromuscular junctions of adult and congenital DM muscle tissues, without any significant changes in structural organisation [32].


**Figure 2 –** The nucleotide sequences and schemes of ID01508.5p-miR binding sites in 5'UTR mRNA *of ADRBK1, BRSK2, C11orf87* and *FMR1* genes

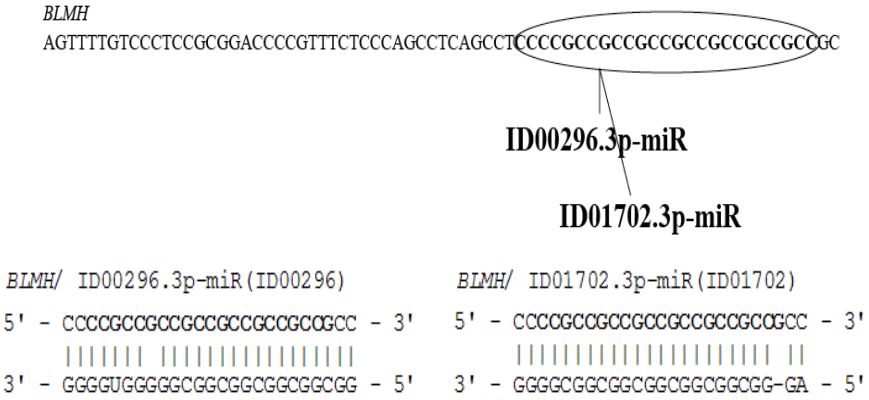


**Figure 3 –** The nucleotide sequences and schemes of ID01702.3p-miR binding sites in 5'UTR mRNA of *BLMH* gene

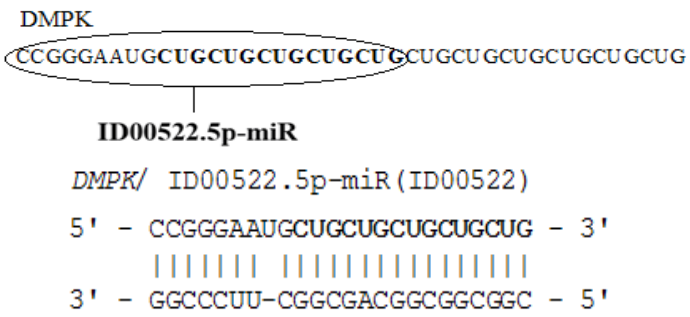


**Figure 4 –** The nucleotide sequence and scheme of ID00522.5p-miR binding site in 3'UTR mRNA of *DMPK* gene

**Table 3 –** Diseases and functions of miRNAs target genes which cause neurological disorders

| Genes | Function | PMID | Disease | PMID |
|---|---|---|---|---|
| *ATXN2* | Ataxin-2 plays roles in a variety of cellular pathways including the maturation, translation and endocytosis of mRNA | 27531668 | 2 spinocerebellar ataxia, amyotrophic lateral sclerosis(ALS) | 25148523 |
| *FMN2* | FMN2 plays an important role in the movement or differentiation of neurons | 30227168 | Intellectual disability, post-traumatic stress disorder, Alzheimer's disease (AD) | 28768717 |
| *MN1* | During embryogenesis, *MN1* plays a key role in the formation of membranous bones in the skull. | 15870292 | C-Terminal Truncation (MCTT) syndrome, intellectual disability (ID) | 31834374 |
| *ADRBK1* | *ADRBK1* plays a crucial role in fundamental cellular functions including cell proliferation , differentiation, and migration | 25279970 | Heart disease and Alzheimer's disease | 30463058 |
| *BRSK2* | *BRSK2* plays a major role in the distribution of synaptic vesicles, the development of synapse and neuronal polarisation | 3448725 | Autism, tuberous sclerosis, developmental delay and intellectual disability (ID) | 30879638 |
| *C11orf87* | The *C11orf87* is primarily expressed in brain tissue, also known as the neuronal integral membrane protein 1 (NEURIM1). | 31959813 | Schizophrenia | 31959813 |
| *FMR1* | The gene *FMR1* encodes FMRP with an amino terminal domain composed of structural modules, a tandem sequence of two domains Agenet / Tudor | 29178241 | Fragile-X syndrome (FXS) | 28176767 |
| *BLMH* | *BLMH* is an essential protective against death caused by Bleomycin and plays an important role in neonatal survival and the maintenance of epidermal integrity. | 10200322 | Alzheimer's disease | 28781776 |
| *DMPK* | The gene *DMPK* plays a major role in muscle, heart and brain cells. | 20301344 | Skeletal muscle neuromuscular and myotendinous junctions, myotonic dystrophy | 8036515 |

## Conclusion

Using the bioinformatic study of the characteristics of the interaction of novel miRNAs with mRNA of genes having trinucleotide repeats has not yet been performed. In the present research, for the first time MirTarget program was used to identify the interaction novel miRNAs with mRNA candidate genes having CAG, CGG, CCG and CUG trinucleotide repeats in coding sequences (CDS) and untranslated regions (UTRs).

We studied the characteristics of the interaction of miRNA with mRNA of genes having trinucleotide repeats. It has been identified five (ID00372.5p-miR, ID01508.5p-miR, ID00296.3p-miR, ID01702.3p-miR and ID00522.5p-miR) key associations of miRNAs and nine gene's mRNAs (*ATXN2, FMN2, MN1, ADRBK1, BRSK2, C11orf87, FMR1, BLMH* and *DMPK*) that have a free energy of interaction of -121 kJ/mole to – 148 kJ/mole.

The binding sites of ID00372.5p-miR, ID01508.5p-miR, ID00296.3p-miR, ID01702.3p-miR and ID00522.5p-miR and their target genes *ATXN2, FMN2, MN1, ADRBK1, BRSK2, C11orf87, FMR1, BLMH* and *DMPK* may be able to provide insights into pathogenesis mechanism and pave the way for the development of new diagnostic markers and therapeutic targets for neurological disorders. Addi-

tionally, the binding sites of the nucleotide sequences of novel miRNAs from Londin *et al.* (Londin, 2015: 1106) [12] with genes were derived from GenBank is not yet fully understood, therefore their function and target genes can be useful for understanding their physiological role in human diseaseas well as paving the way for new researches in the future studies. The research results can be used as a unified database as a basis for further experiments with animals and humans in biotechnology and medicine for early diagnosis, prevention and treatment of neurodegenerative diseases.

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