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A. M. Belkozhayev, R. Ye. Niyazova

Al-Farabi Kazakh National University, Almaty, Kazakhstan.
E-mail: ayaz_jarkent@mail.ru, raygul.nyiyazova@kaznu.kz

THE INTERACTION OF miR-4258, miR-3960, miR-211-3p AND miR-3155b WITH mRNAs GENES OF NON-POLYGLUTAMINE TRINUCLEOTIDE DISORDERS

Abstract. Trinucleotide repeat expansion disorders constitute a group of dominantly inherited neurological diseases that are incurable and ultimately fatal. In the present work, miRNA binding sites were predicted by the MirTarget program. It was given characteristics of miRNAs binding sites in 5' and 3' UTR mRNAs genes of non-polyglutamine trinucleotide disorders with CGG, GCC, CUG repeats. Binding sites of 2567 miRNAs with mRNAs of 17494 human genes were determined. 206 genes with nucleotide repeats, mRNAs of which are bind with miRNA in the 5'UTR and 3'UTR, were observed. From thus, 2668 miRNAs binding sites are located in the 5'UTR, 3853 – in the 3'UTR with ΔG/ΔGm values equal to 85 % and more. It was found that 34 gene's mRNA having trinucleotide (CGG\GCC\CUG) repeats were targets for miR-4258, miR-3960 miR-211-3p and miR-3155b. miR-4258 binds to mRNA of *ADARB1, C11orf87* and *CBFB* genes with free binding energy - 93 kJ/mole and ΔG/ΔGm 91%, to mRNA of *ARHGEF7, BCR, BRSK2* and *C9orf91* genes with free binding energy - 91 kJ/mole and ΔG/ΔGm 89%. miR-3960 binds in GCC repeats to mRNA of *ABCC1* and *BLMH* genes with free binding energy - 116 kJ/mole. miR-211-3p and miR-3155b interact with mRNA of *ACACA* and *ANKRD13D* genes in 5'-3'untranslated regions. Studying binding characteristics of miRNA and genes will help identify association of miRNAs with genes with trinucleotide repeats for recommending for the diagnosis of nucleotide repeat expansion disorders.

Key words: miRNA, mRNA, binding site, trinucleotide repeat expansion.

Introduction. Trinucleotide repeats are sets of three nucleotides present in succession in various copy numbers throughout the human genome [1]. Repetitive sequences of genetic code are quite common. However, when these sequences grow beyond the scope of what would be considered normal, they cause disease. While the human genome has mechanisms to protect against these expansions, patients present with what can be severe neuromuscular and neurodegenerative disorders. There have been many diseases discovered by TNR (trinucleotide repeat) expansions, but the most prominent are spinocerebellar ataxia, Huntington disease, Fragile X syndrome, myotonic dystrophy, and Friedrich ataxia [2].

Small regulatory RNAs, particularly miRNAs, are known to be dynamically regulated in neurogenesis and brain development. Some recent studies have suggested that the alterations in small regulatory RNAs could contribute to the pathogenesis of several neurodevelopmental disorders [3,4]. miRNA refers to a small non-coding, single stranded RNA molecule comprising of around 22 nucleotides. By base pairing to messenger RNA (mRNA) and triggering translation repression, the miRNAs control gene

expression [5]. The use of miRNA as biomarkers to help diagnose neurodegenerative disorders offers several advantages. As the expression of miRNAs are commonly altered during disease, they have gained much attention for their potential use as biomarkers [6]. With better understanding of the role of miRNAs in neurodegenerative diseases, scientists and researchers may create effective new drugs to treat these devastating human illnesses. However, the biological function of most miRNAs remains to be uncovered [7, 8]. It is therefore important to provide characteristics of miRNA interaction with mRNA genes associated with non-polyglutamine trinucleotide disorders.

Materials and methods. The nucleotide sequences of mRNAs of human genes were downloaded from NCBI (http://www.ncbi.nlm.nih.gov). The nucleotide sequences of human miRNAs were downloaded from the miRBase database (http://mirbase.org). The miRNAs binding sites in mRNAs of several genes were predicted using the MirTarget program [9]. This program defines the following features of miRNA binding to mRNA: a) the start of the initiation of miRNA binding to mRNAs; b) the localization of miRNA BS in 5′UTRs, CDSs and 3′UTRs of the mRNAs; c) the free energy of interaction miRNA and the mRNA (ΔG, kJ/mole); d) the schemes of nucleotide interactions between miRNAs and mRNAs. For analyzing and formatting sequences of genes, we used the sequence manipulation suite program (https:// bioinformatics.org/sms). To prediction the secondary structure of RNA, the software RNA fold was used (http://rna.tbi.univie. ac.at) [10].

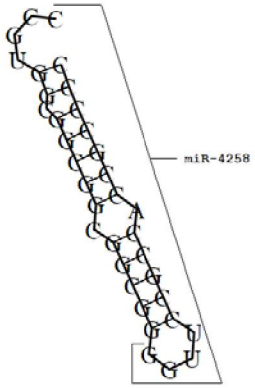
Results and discussion. Using the MirTarget program, the binding sites of 2567 miRNA with the mRNA of 17494 human genes were determined. 206 genes with nucleotide repeats, the mRNAs of which are bind with miRNA in the 5'UTR and 3'UTR, were observed. 2668 miRNAs binding sites are located in the 5'UTR, 3853 – in the 3'UTR with ΔG/ΔGm values equal to 85 % and more. Only miR-4258, miR-3960 miR-211-3p and miR-3155b bind with 34 gene's mRNA having trinucleotide CGG, GCC, CUG repeats causing non - polyglutamine disorders. In table 1-3 are shown characteristics of miRNA binding with mRNA genes having trinucleotide repeats in 5'-UTR and 3'-UTR. The mRNA of *ABL2, ACVR1B, ADARB1, ADRBK1, APBA1, ARHGEF7, FMR1, B4GALT2, BCL11B, BCR, BRSK2, BRWD1, BTBD7, C11orf87, C9orf91, CACNA1A, CADM4, CAMK4, CARM1, CBFB, CBL* and *CCDC93* genes having trinucleotide repeats interact with miR-4258 in 5'-UTR in regions with CGG repeat. The binding sites of miR-3960 in mRNA of*ABCC1, ABCD3, AFF2, ANKH, ANKRD13D, BCL11A, BCL2L11, BLMH, C4orf19* and *CA10* genes are located in 5'-UTR in regions with GCC repeat. mRNA of *ACACA* and *ANKRD13D* genes interact with miR-211-3p and miR-3155b in 5'-UTR / 3'-UTR in regions with CUG repeat.

Table 1 – Characteristics of miR-4258 binding sites
in the 5'-UTR mRNA genes having CGG trinucleotide repeat

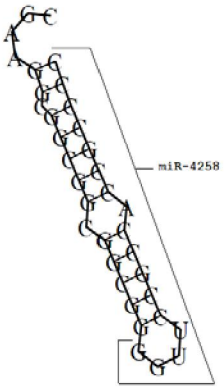
Gene	Beginning of binding site	ΔG, kJ/mole	ΔG/ΔGm, %	Scheme of miRNA binding with mRNA genes
ABL2	21	-89	87	5' – CGGCGGCGGUGGCGGCGG – 3' || |||||||||| || 3' – GGUUCCGCCACCGCC-CC – 5'
ACVR1B	46	-89	87	5' – CGGCGGCGGUGGCGGCGG – 3' || |||||||||| || 3' – GGUUCCGCCACCGCC-CC – 5'
ADARB1	18	-93	91	5' – CCGUGG**CGGCGGCGGCGG** – 3' ||| |||||||||| || 3' – GGUUCCGCCACCGCC-CC – 5'
ADRBK1	7	-87	85	5' – CGCGGG**CGGCGGCGGCGG** – 3' 	|||||||||| || 3' – GGUUCCGCCACCGCC-CC – 5'
APBA1	50	-87	85	5' – UCC**CGGCGGCGGCGGCGG** – 3' || |||||||||| || 3' – GGUUCCGCCACCGCC-CC – 5'
ARHGEF7	155	-91	89	5' – GCGAGG**CGGCGGCGGCGG** – 3' |||||||||||||| || 3' – GGUUCCGCCACCGCC-CC – 5'

FMR1	98	-87	85	5' - GCG**CGGCGGCGGCGGCGG** - 3' || |||||||||||| || 3' - GGUUCCGCCACCGCC-CC - 5'
B4GALT2	133	-87	85	5' - CCCG**CGGCGGCGGCGG**CG - 3' ||	|||||||||||| | 3' - GGUU-CCGCCACCGCCCC - 5'
BCL11B	150	-87	85	5' - **CGGCGGCGGCGGCGGCGG** - 3' |	|||||||||||| || 3' - GGUUCCGCCACCGCC-CC - 5'
BCR	200	-91	89	5' - CCGAGGAGG**CGGCGGCGG** - 3' |||||| ||||||||| || 3' - GGUUCCGCCACCGCC-CC - 5'
BRSK2	100	-91	89	5' - CCU**CGGCGGCGGCGGCGG** - 3' || |||||||||||| || 3' - GGUUCCGCCACCGCC-CC - 5'
BRWD1	175	-87	85	5' - **CGGCGGCGGCGGCGGCGG** - 3' |	|||||||||||| || 3' - GGUUCCGCCACCGCC-CC - 5'
BTBD7	87	-87	85	5' - **CGGCGGCGGCGGCGG**UGG - 3' |	|||||||||||| || 3' - GGUUCCGCCACCGCC-CC - 5'
C11orf87	11	-93	91	5' - CGAAGG**CGGCGGCGGCGG** - 3' | ||||||||||||| || 3' - GGUUCCGCCACCGCC-CC - 5'
C9orf91	10)	-91	89	5' - CCGGGGUGG**CGGCGGCGG** - 3' |||||||||||||| || 3' - GGUUCCGCCACCGCC-CC - 5'
CACNA1A	158	-87	85	5' - UCAG**CGGCGGCGGCGG**CG - 3' |||| |||||||||||| | 3' - GGUU-CCGCCACCGCCCC - 5'
CADM4	27	-87	85	5' - **CGGCGGCGGCGGCGGCGG** - 3' |	|||||||||||| || 3' - GGUUCCGCCACCGCC-CC - 5'
CAMK4	90	-87	85	5' - CGCGGG**CGGCGGCGG**UGG - 3' | |||||||||||| || 3' - GGUUCCGCCACCGCC-CC - 5'
CARM1	12	-87	85	5' - CAG**CGGCGGCGGCGGCGG** - 3' |	|||||||||||| || 3' - GGUUCCGCCACCGCC-CC - 5'
CBFB	39	-93	91	5' - CUGAGG**CGGCGGCGGCGG** - 3' |||||||||||||| || 3' - GGUUCCGCCACCGCC-CC - 5'
CBL	14	-89	87	5' - CCGG**CGGCGGCGGCGG**CG - 3' |||| |||||||||||| | 3' - GGUU-CCGCCACCGCCCC - 5'
CCDC93	33	-87	85	5' - **CGGCGGCGGCGGCGGCGG** - 3' |	|||||||||||| || 3' - GGUUCCGCCACCGCC-CC - 5'

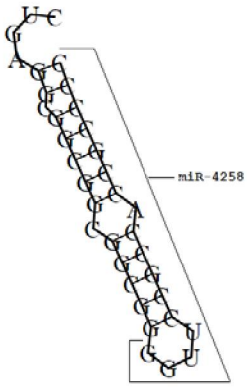
According to the table 1 only mRNA of *ADARB1*, *C11orf87* and *CBFB* genes have miR-4258 binding sites with free binding energy – 93 kJ/mole with the ΔG/ΔGm values equal to 91%. miR-4258 binds to CGG repeats of *ADARB1* gene in repeat nucleotide sequences CGG_{10}. The binding sites are located between 15 and 62 repeat nucleotide sequences with start in 18 nt. The binding sites of miR-4258 in mRNA of *C11orf87* and *CBFB* genes are located in repeat nucleotide sequences CGG_{10} /CGG_8 between 5-40 and 36-65 with start in 11 and 39 nt, respectively free binding energy equal to – 93 kJ/mole (figure 1). The secondary structures given in the figure clearly show the preferential formation of bonds with miR-4258.



A- mir-4258 binding site in mRNA *ADARB* gene



B - mir-4258 binding site in mRNA *C11orf87*gene



C -mir-4258 binding site in mRNA *CBFB*gene

Figure 1 – Secondary structures of location of mir-4258 binding sites in 5' UTR mRNA of *ADARB, C11orf87* and *CBFB* genes

It was known that *ADARB1* gene encodes an RNA editing enzyme, expressed mainly in the central nervous system (CNS), which is involved in the downstream regulation of neuro transmitters. *ADARB1* (also known as *ADAR2*) spans a genomic region of 25 kb on chromosome 21q22.3 and comprises 16 exons and regulates its own expression through self-editing [11]. It was demonstrated that mRNA of *ARHGEF7, BCR, BRSK2* and *C9orf91* genes interact with miR-4258 with free binding energy – 91 kJ/mole and ΔG/ΔGm values equal to 89%.

Table 2 – Characteristics of miR-3960 binding sites in the 5'-UTR mRNA genes having GCC trinucleotide repeat

Gene	Beginning of binding site	ΔG, kJ/mole	ΔG/ΔGm, %	Scheme of miRNA binding with mRNA genes
ABCC1	31	-116	93	5' – CCCUGC**GCCGCCGCCGCCGCC** – 3' |||| |||| |||||||||| 3' – GGGG-GCGGAGGCGGCGGCGG – 5'
ABCD3	46	-114	91	5' – **GCCGCCGCCGCCGCCGCCGCC** – 3' || ||||| |||||||||| 3' – GGG-GGCGGAGGCGGCGGCGG – 5'
AFF2	14	-110	88	5' – GCCGCU**GCCGCCGCCGCCGCC** – 3' || ||||| |||||||||| 3' – GGG-GGCGGAGGCGGCGGCGG – 5'
ANKH	34	-112	89	5' – CCUUCU**GCCGCCGCCGCCGCC** – 3' ||| ||||| |||||||||| 3' – GGG-GGCGGAGGCGGCGGCGG – 5'
ANKRD13D	19	-108	86	5' – CCU**GCCGCCC**GCGCU**GCCGCC** – 3' ||| |||||| |||||||||| 3' – GGG-GGCGGAGGCGGCGGCGG – 5'
BCL11A	177	-112	89	5' – CGUCCGCCC**GCCGCCGCCGCC** – 3' | ||||||| |||||||||| 3' – GGGGGCGGA-GGCGGCGGCGG – 5'
BCL2L11	61	-110	88	5' – GCCGCU**GCCGCCGCCGCCGCC** – 3' || ||||| |||||||||| 3' – GGG-GGCGGAGGCGGCGGCGG – 5'
BLMH	182	-116	93	5' – CUCCCC**GCCGCCGCCGCCGCC** – 3' ||||| ||| |||||||||| 3' – GGGGG-CGGAGGCGGCGGCGG – 5'
C4orf19	73	-108	86	5' – GACCCC**GCCGCCGCCGCCGCC** – 3' ||| ||| |||||||||| 3' – GGGGG-CGGAGGCGGCGGCGG – 5'
CA10	772	-110	88	5' – GCUGCC**GCCGCCGCCGCCGCC** – 3' || ||||| |||||||||| 3' – GGG-GGCGGAGGCGGCGGCGG – 5'

It can be seen from the table 2 that the free energy of the interaction of the miR-3960 with mRNA of *ABCC1, ABCD3, AFF2, ANKH, ANKRD13D, BCL11A, BCL2L11, BLMH, C4orf19* and *CA10* genes are constituted more than - 108 kJ/mole with ΔG/ΔGm values equal to 86 -91%. Among mRNA genes having nucleotide GCC repeats only *ABCC1* and *BLMH* genes bind with high free energy - 116 kJ/mole with miR-3960. miR-3960 binding sites are located in region with GCC_7 and GCC_8 repeats between 31 (beginning of binding sites) – 57 and 182 (beginning of binding sites) – 211 nt (figure 2). The secondary structures given in the figure clearly show the preferential formation of bonds with miR-3960. The mRNA gene of *ABCD3* interact with miR-3960 with full GCC_7 repeat. However, the binding sites of miR-3960 and mRNA genes of *ANKH (*GCC_5), *ANKRD13D* (GCC_4) and *BCL11A* (GCC_4) have only four and five GCC repeat.

A - mir-3960 binding site in mRNA *ABCC1* gene

B - mir-3960 binding site in mRNA *BLMH* gene

Figure 2 – Secondary structures of location of miR-3960 binding sites in 5'UTR mRNA of *ABCC1* and *BLMH* genes

ABCC1 (*MRP1*) is well known for its role in rendering cancer cells resistant to chemotherapy. ABCC1 is expressed in brain capillaries on the abluminal surface between the luminal membrane (CD31) and astrocytic end-feet (GFAP). Moreover, the free energy of miR-3960 interaction with mRNA gene of *ABCD3* indicate –114kJ/mole with ΔG/ΔGm values equal to 91%. *ABCD3* is one of the most abundant peroxisomal membrane proteins, at least in hepatocytes, and has been reported to be involved in the transport of various fatty acids. Mutation in *ABCD3* have been found in two individuals affected by Zellweger syndrome.

Table 3 – Characteristics of miR-211-3p, miR-3155b binding sites in 5'-UTR and 3'-UTR mRNA genes having CUG trinucleotide repeat

Gene	miRNA	Region	Beginning of binding site	ΔG, kJ/mole	ΔG/ΔGm, %	Scheme of miRNA binding with mRNA genes
ACACA	miR-211-3p	5'UTR	61	-101	85	5' – GCGCGC**CUGCUGCUG**UCCCCGU – 3' |||| ||| |||||||||||| 3' – CGUGGGGA-AACGACAGGGACG – 5'
ANKRD 13D	miR-3155b	3'UTR	2056	-87	85	5' – UCU**CUGCUGCUG**AGCUUGG – 3' |||| ||||| |||||||| 3' – AGGG-UGACGUCUCGGACC – 5'

From the table 3 obtained data indicate that miR-211-3p and miR-3155b interact with mRNA of *ACACA* and *ANKRD13D* genes in 5'-3'untranslated regions. miR-211-3p binding site in the 5'UTR mRNA of *ACACA* gene is located from 61 to 82 nt with $(CUG)_3$ repeat. miR-211-3p interact with high free energy -101 kJ/mole mRNA of *ACACA* gene.

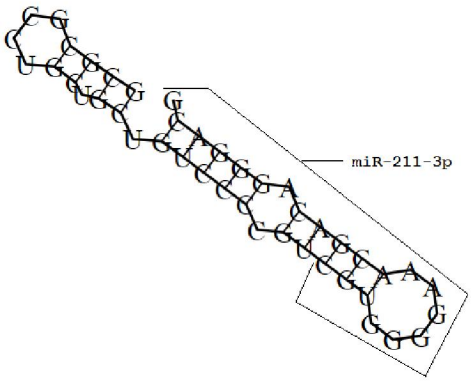


Figure 3 – Secondary structures of miR-211-3p binding sites location in 5'UTR mRNA of *ACACA* gene

Thus, the obtained results show that the greater number of genes are targets for miR-4258. miR-4258 binds to mRNA of 22 genes (*ABL2, ACVR1B, ADARB1, ADRBK1, APBA1, ARHGEF7, FMR1, B4GALT2, BCL11B, BCR, BRSK2, BRWD1, BTBD7, C11orf87, C9orf91, CACNA1A, CADM4, CAMK4, CARM1, CBFB, CBL* and *CCDC93*) with free binding energy -89 kJ/mole -(-93 kJ/mole) and ΔG/ΔGm value from 85% to 91%. Moreover, the binding sites of miR-3960 in mRNAs of *ABCC1, ABCD3, AFF2, ANKH, ANKRD13D, BCL11A, BCL2L11, BLMH, C4orf19* and *CA10* genes have highest free binding energy from -108 kJ/mole to -116 kJ/mole and ΔG/ΔGm value from 86% to 93%. The maximum free energy of miR-3960 binding to mRNA is -116 kJ/mole. miR-3960 plays an important role in osteogenic transdifferentiation of vascular smooth muscle cells (VSMCs) and contributes to vascular calcification [12]. miR-3960 has 1100 binding sites on 375 target mRNAs with $\Delta G/\Delta G_m$ values of 90% or more and belong to a group of unique miRNAs [13].

Conclusion. In this paper, we have presented characteristics of predicted binding sites of miRNAs with mRNA genes of non - polyglutamine trinucleotide disorders. The most interesting data concern the analysis of target genes of miR-4258, miR-3960 miR-211-3p and miR-3155b. The identified associations of these miRNAs and target genes can be used to develop molecular methods for the neurological disease diagnosis. Also to date, there is a limited researches on nucleotide repeats. Therefore, further analysis using interaction of miRNAs with mRNA genes of all nucleotide repeats (di-, tri-, tetra-, penta-) including CDS region may be very useful to obtain advances knowledge.

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А. М. Белкожаев, Р. Е. Ниязова

Әл-Фараби атындағы Қазақ ұлттық университеті, Алматы, Қазақстан

ПОЛИГЛУТАМИНДІ ЕМЕС ТРИНУКЛЕОТИДТІК БҰЗЫЛЫСТЫ ГЕНДЕРДІҢ Mrna-МЕН miR-4258, miR-3960, miR-211-3P ЖӘНЕ miR-3155b-ЛАРДЫҢ ӨЗАРА ӘРЕКЕТТЕСУІ

Аннотация. Тринуклеотидтік қайталанымды экспансия бұзылыстары емделмейтін, ақыр соңында өлімге әкеліп соғатын неврологиялық тұқым қуалайтын аурулар тобын құрайды. Жұмыс барысында miRNA-дың байланысатын сайттары MirTarget бағдарламасы арқылы болжанды. Бұл бағдарлама келесілерді анықтайды: miRNA-ның mRNA-мен байланыстыратын сайттарының басталуын; 5'UTR, CDS және 3'UTR-де mRNA сайттарының орналасуы; бос байланысу энергиясы (ΔG, кДж/моль) және miRNA-ның нуклеотидтерінің mRNA-мен әрекеттесу схемалары. Әр аймақ үшін ΔG/ΔGm қатынасы (%) есептелді, мұндағы ΔGm нуклеотидтердің толық тізбегі бар miRNA-ның бос байланыс энергиясына тең. Гендердің барлық нуклеотидтік тізбегі GenBank-тан алынды (http://www.ncbi.nlm.nih.gov). miRNA нуклеотидтер тізбегі miRBase мәліметтер базасынан алынды (http://www.mirbase.org). miRNA-гендік экспрессияны транскрипциядан кейінгі реттеуде маңызды рөл атқаратын, кодталмаған РНҚ-ның үлкен тобы. CGG, GCC, CUG қайталанатын полиглутаминдік емес тринуклеотидті бұзылыстардың 5' және 3' UTR-де гендердің mRNA-мен miRNA-дың байланысатын сайттарына сипаттама берілді. 2567 miRNA-дың 17494 адам гендерінің mRNA-мен байланысатын

сайттары анықталды. 5'UTR және 3'UTR-де mRNA-лары miRNA-мен байланысқан нуклеотидтердің қайталануы бар 206 ген байқалды. Осылайша, 5'UTR-де 2668, 3'UTR-де 3853 miRNA-мен байланысатын сайттар 85 % және одан да көп ΔG / ΔGm мәндерде орналасқан. Тринуклеотидтік CGG, GCC, CUG қайталануы бар 34 геннің mRNA-лары miR-4258, miR-3960 miR-211-3p және miR-3155b-ларына нысан екендігі анықталды. *ADARB1, C11orf87* және *CBFB* гендердің mRNA-ларының бос энергиясы ΔG/ΔGm 91 % мәнінде – 93 кДж/моль-ға тең, сонымен қатар *ARHGEF7, BCR, BRSK2* және *C9orf91* гендердің mRNA-ларының бос байланысатын энергиясы ΔG/ΔGm 89 % мәнінде – 91 кДж / моль-ға тең, miR-4258-бен байланысады. *ABCC1* және *BLMH* гендерінің mRNA-ларының GCC қайталанымдары бос байланысатын энергиясы – 116 kJ/mole болатын miR-3960-бен байланысады. miR-3960 байланыстыру сайттары GCC_7 және GCC_8 қайталанатын 31 аймақта орналасқан (байланыстыру сайттарының басталуы) – 57 және 182 (байланыстыру сайттарының басталуы) – 211 nt. GCC_7-қайталымның толық қайталануымен, *ABCD3* генінің mRNA-сы miR-3960-пен өзара әрекеттеседі. Дегенмен miR-3960 және *ANKH* (GCC_5), *ANKRD13D* (GCC_4) және *BCL11A* (GCC_4) гендерінің байланысу сайттарында тек төрт және бес GCC қайталануы бар. miR-3960-375 гендердің mRNA нысандарында ΔG/ΔGm 90 % үлесінде 1100 сайтпен байланысады немесе одан жоғары нысандарға арналған байланысу сайттары бар және ерекше miRNA тобына жатады. 5’ және 3’'UTR-де *ACACA* және *ANKRD13D* гендерінің mRNA-лары miR-211-3p және miR-3155b-мен өзара әрекеттеседі. *ACACA* гендерінің mRNA-лары 5'UTR-де miR-211-3p-пен байланысуы 61-ден 82 нт аралығында $(CUG)_3$ қайталануымен орналасқан. miR-211-3p жоғары бос энергиямен mRNA-да – 101 кДж/моль есебімен *ACACA* генімен әрекеттеседі. miRNA-лармен гендердің байланысу сипаттарын зерттеу нуклеотидтік қайталанатын экспансиялық бұзылыстарды диагностикалауда miRNA-мен ассоциациясын анықтауға көмектеседі.

Түйін сөздер: miRNA, mRNA, байланысатын сайт, тринуклеотидті қайталанатын экспансия.

А. М. Белкожаев, Р. Е. Ниязова

Казахский национальный университет им. аль-Фараби, Алматы, Казахстан

ВЗАИМОДЕЙСТВИЕ miR-4258, miR-3960, miR-211-3P И miR-3155b С mRNA ГЕНОВ НЕПОЛИГЛУТАМИНОВЫХ ТРИНУКЛЕОТИДНЫХ РАССТРОЙСТВ

Аннотация. Расстройства экспансии тринуклеотидных повторов представляют собой группу доминантно-наследуемых неврологических заболеваний, которые неизлечимы и в конечном итоге приводят к летальному исходу. Изменение экспрессии miRNA считается отличительным признаком многих заболеваний, включая нарушения экспансии тринуклеотидных повторов. В настоящей работе сайты связывания miRNA были предсказаны программой MirTarget. Программа определяет: начало сайтов связывания miRNA с mRNA; расположение сайтов в 5'UTR, в CDS и в 3'UTR mRNA; свободную энергию гибридизации (ΔG, kJ/mole) и схемы взаимодействия нуклеотидов miRNA с mRNA. Для каждого сайта рассчитывали отношение ΔG/ΔGm (%), где ΔGm равна свободной энергии связывания miRNA с полностью комплементарной нуклеотидной последовательностью. Все нуклеотидные последовательности mRNA генов заимствовали из GenBank (http://www.ncbi.nlm.nih.gov). Нуклеотидные последовательности miRNA получены из базы miRBase (http://www.mirbase.org). miRNA представляет собой большое семейство консервативных некодирующих РНК, играющих ключевую роль в посттранскрипционной регуляции экспрессии генов. Приведены характеристики сайтов связывания miRNA в 5'UTR и 3'UTR mRNA генов неполиглутаминовых тринуклеотидных расстройств с повторами CGG, GCC, CUG. Были определены сайты связывания 2567 miRNA с mRNA 17494 генов человека. Было обнаружено 206 генов с нуклеотидными повторами, mRNA которых связывались с miRNA в 5'UTR и 3'UTR. Таким образом, 2668 сайта связывания miRNAs расположены в 5'UTR, 3853 - в 3'UTR со значениями ΔG/ΔGm, равными 85% и более. Было обнаружено, что mRNA 34 генов, имеющих тринуклеотидные CGG, GCC, CUG повторы, были мишенью для miR-4258, miR-3960 miR-211-3p и miR-3155b. miR-4258 связывается с mRNA генов *ADARB1, C11orf87* и *CBFB* со свободной энергией взаимодействия - 93 кДж/моль и ΔG/ΔGm 91%, с mRNA генов *ARHGEF7, BCR, BRSK2* и *C9orf91* со свободной энергией взаимодействия - 91 кДж/моль и ΔG/ΔGm 89%. miR-3960 связывается в повторах GCC с mRNA генов *ABCC1* и *BLMH* со свободной энергией взаимодействия - 116 кДж/моль. Сайты связывания miR-3960 расположены в области с повторами GCC_7 и GCC_8 между 31 (начало сайтов связывания) - 57 и 182 (начало сайтов связывания) - 211 нт. mRNA гена *ABCD3* взаимодействует с miR-3960 с полным повтором GCC_7. Однако сайты связывания генов miR-3960 и mRNA генов *ANKH* (GCC_5), *ANKRD13D* (GCC_4) и *BCL11A* (GCC_4) имеют только четыре и пять повторов GCC. miR-3960 имеет 1100 сайтов связывания на 375 mRNA - мишенях со значениями ΔG / ΔGm 90% и более и относятся к группе уникальных miRNA. miR-211-3p и

miR-3155b взаимодействуют с mRNA генов *ACACA* и *ANKRD13D* в 5'-3'-нетранслируемых областях. Сайт связывания miR-211-3p в 5'UTR mRNA генов *ACACA* расположен от 61 до 82 нт с повторением $(CUG)_3$. miR-211-3p взаимодействует с mRNA высокой свободной энергии -101 кДж / моль гена *ACACA*. Изучение характеристик связывания miRNA и генов поможет выявить связь miRNA с генами с тринуклеотидными повторами для рекомендации для диагностики нарушений экспансии нуклеотидных повторов.

Ключевые слова: miRNA, mRNA, сайт связывания, экспансия тринуклеотидных повторов.

Information about authors:

Belkozhayev A.M., PhD-student, al-Farabi Kazakh National University, Almaty, Kazakhstan; ayaz_jarkent@mail.ru; https://orcid.org/0000-0001-7429-4994

Niyazova R.Ye., c.b.s. professor; al-Farabi Kazakh National University, Scientific research institute of biology and biotechnology problems, Almaty, Kazakhstan; raygul.nyiyazova@kaznu.kz; https://orcid.org/0000-0002-7946-1189

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