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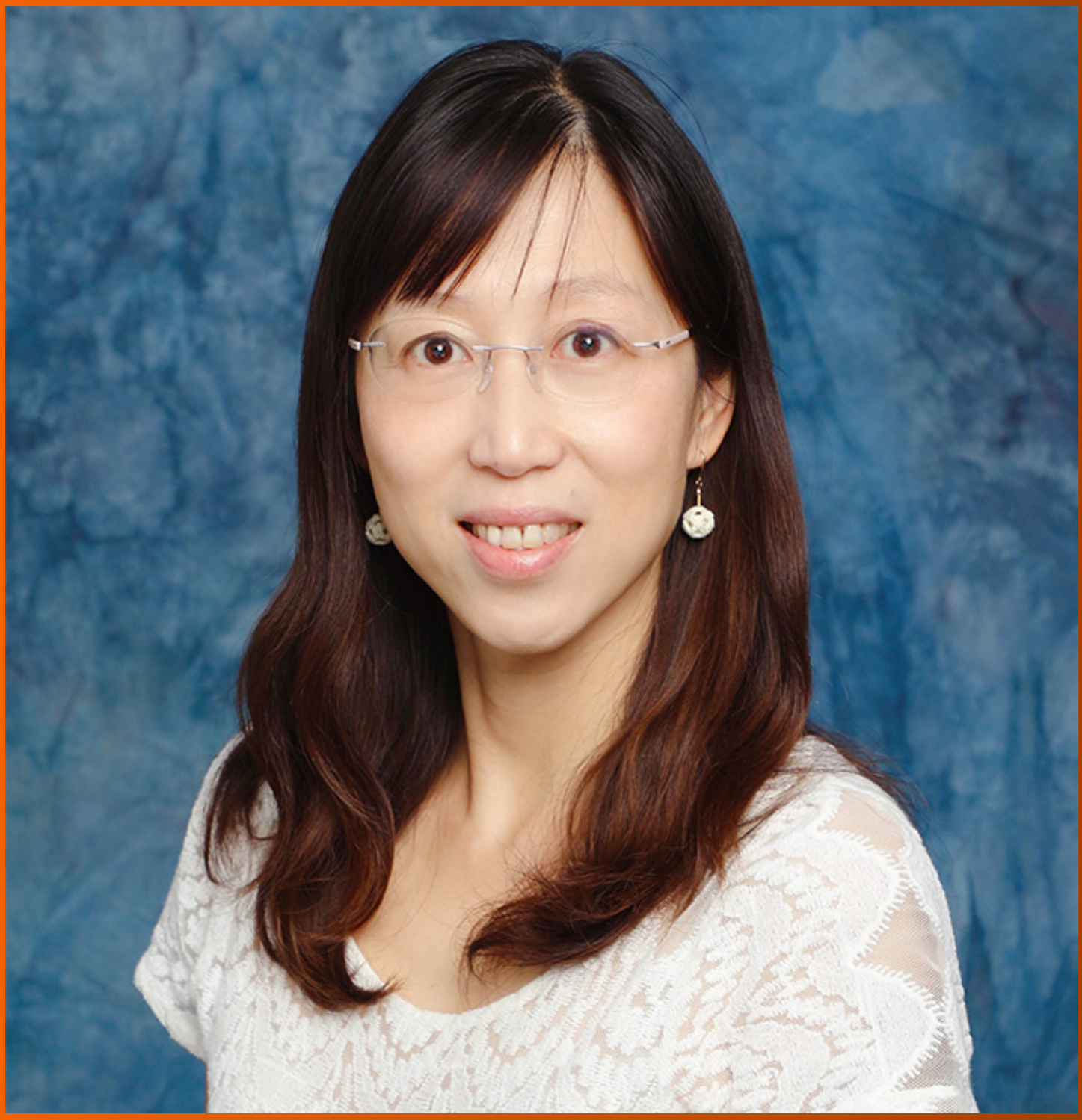

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FIELD OF VISION

Identification of miR-802-5p and its involvement in type 2 diabetes mellitus

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Abstract

MicroRNAs (miRNA) are recently discovered endogenous, small noncoding RNAs (of 22 nucleotides) that play pivotal roles in gene regulation. They are involved in post-transcriptional control of gene expression. miRNAs are emerging as important regulators of cell proliferation, development, cancer formation, stress responses, cell death and physiological conditions. Increasing evidence has demonstrated the human miRNAs bind to their target mRNA sequences with perfect or near-perfect sequence complementarily. This provides a powerful strategy for discovering potential type 2 diabetes mellitus (T2DM) targets and gives the probability to exploit them for diagnostic and therapeutic causes. About 6% of the world population is affected by T2DM, and it is recognized as a global epidemic by the World Health Organization. At present there is no valid biomarker to control or manage T2DM. Therefore, the present study applied a mature sequence of miRNAs from publicly accessible databases to identify the miRNA from T2DM expressed sequence tags, and the results are detailed and discussed below.

Key Words: MicroRNAs; Type 2 diabetes mellitus; miR-802-5p; Biomarker; Expressed sequence tags; Disease

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Core Tip: MicroRNAs (miRNA) are endogenous, small noncoding RNAs that play pivotal roles in gene regulation. They are involved in post-transcriptional control of gene expression and are important regulators of cell proliferation, development, cancer formation, stress responses, cell death and physiological conditions. About 6% of the world population is affected by type 2 diabetes mellitus. It is recognized as a global epidemic. At present there is no valid biomarker to control or manage type 2 diabetes mellitus. The present study applied a mature sequence of miRNAs from publicly accessible databases to identify miRNAs from type 2 diabetes mellitus expressed sequence tags.

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INTRODUCTION

MicroRNAs (miRNA) are recently discovered endogenous, small noncoding RNAs (of 22 nucleotides) that play pivotal roles in gene regulations[1]. They are involved in post-transcriptional control of gene expression. miRNAs are emerging as important regulators of cell proliferation, development, cancer formation, stress responses, cell death and physiological conditions[2]. These circulating miRNAs are detected in body fluids including saliva, urine and blood. miRNAs regulate gene control and a variety of biological and metabolic processes[3]. Gaining insight into the miRNA targets will help us to understand the spectrum of miRNA regulation and elucidate the functional importance of miRNAs[4]. Increasing evidence has demonstrated that human miRNAs bind to their target mRNA sequences with perfect or near-perfect sequence complementarily. This provides a powerful strategy for discovering potential type 2 diabetes mellitus (T2DM) targets and gives the probability to exploit them for diagnostic and therapeutic causes[5].

T2DM is known as adult-onset diabetes, a systemic chronic disease of heterogeneous origin[6]. About 6% of the world population is affected by T2DM, and it is recognized as a global epidemic by the World Health Organization[7]. It is characterized by insulin resistance and delayed insulin secretion[8,9]. At present, the management and treatment strategies for T2DM are elusive, and the exact molecular mechanism is not yet completely discovered. Many reports suggest that miRNAs are a promising tool for the management and treatment of various diseases.

On the other side, expressed sequence tags (ESTs) are a simple segment of a sequence from a cDNA clone that correspond to an mRNA. ESTs longer than 150bp were found to be the most useful for similarity searches and mapping[10]. At present there is no valid biomarker to control or manage T2DM. The present study applied a mature sequence of microRNAs from publicly accessible databases to identify the microRNA from T2DM ESTs, and the results are detailed and discussed below.

MATERIALS AND METHODS

EST sequence data was obtained through the National Center for Biotechnology Information web portal for International Nucleotide Sequence Database Consortium. The search term keyword "type-2 diabetes mellitus in *Homo sapiens*" (18271 ESTs as of April 2020) were extracted using this free search engine. Human mature miRNAs were selected out of 38589 entries from miRbase (http://www.mirbase.org/). After removing the low-quality sequences, local nucleotide database was formed for T2DM specific EST sequences[11]. The above-mentioned nucleotide database was searched for the homolog among the miRNAs dataset. The mature miRNAs were used as a source to search for similar T2DM ESTs.

Reference miRNA sequences were used as a query for homology search against the specific T2DM nucleotide sequence database at the e-value threshold < 0.01 using the BLAST program with all other parameters as default. The FASTA formats of all

sequences were processed, and mature miRNA sequences were aligned against the unique ESTs using the ClustalW multiple sequence alignment tool[11,12].

Selected EST sequences with not more than five mismatches were valid for this nonprotein encoding phenomenon using BLAST against the protein database at the National Center for Biotechnology Information using BLASTx with a default parameter[11,12] EST sequences were aligned to reference pre-miRNA sequences. Then the aligned portion was expressed as candidate pre-miRNA sequence[11]. Figure 1 shows the secondary structure of identified hsa-miR-802-5p. The incorporated pre-miRNAs were confirmed for secondary structure using mFold (http://www.mfold.rna.albary.edu/).

While selecting the RNA sequence from the EST resource as a candidate miRNA, the following criteria were referred as per Priyanka *et al*[11]: (1) RNA sequence must fold into an appropriate stem-loop hairpin 2D structure; (2) Mature miRNA sequence site in one arm of the hairpin structure; (3) miRNAs should have less than seven mismatches with the opposite miRNAs* sequence in the other arm; and (4) Predicted 2D structures have higher negative energy minimal free energy (≤ -18 kcal/mol). The prediction of miR-802-5p targets was determined using Target Scan. Table 1 represents the characteristics of a mature miR-802-5p.

RESULTS AND DISCUSSION

To validate this research paper, the available human T2DM ESTs were selected from the National Center for Biotechnology Information EST database for miR-802-5p and evaluated through the bioinformatics approach. The methodology for the identification of miR-802-5p was carried out as described by Priyanka *et al*[11] and Bai *et al*[12]. The source sequences, length of the precursor sequences, minimum folding energy and A + U content of the predicted miRNA are shown in Table 1. Secondary structural analysis of the pre-miRNA related sequence of the noncoding ESTs revealed the presence of miR-802-5p as shown in Figure 1. The minimum folding free energy was -37.90. It contained 61% A + U. From the above findings, it is clearly evident that miR-802-5p is present in T2DM ESTs, suggesting that it might have clinical relevance with disease progression. In addition, miRNA target analysis has been analyzed by the Target Scan online computational tool (http://www.targetscan.org/vert_72/) to identify miR-802-5p targets. Table 2 represents the identified targets for miR-802-5p.

CONCLUSION

In conclusion, miR-802-5p, a novel miRNA has been identified from human T2DM through a computational approach. However, further studies about miR-802-5p are required to prove how it is involved in the suppression and progression of T2DM. This computational approach proves the role of miRNAs and creates the platform for further research studies both *in vitro* and *in vivo*.

Table 1 Represents the characteristics of mature miR- 802-5p

Source miRNA	Source organism	PL	MFE Δ G	MS	Strand	A + U, %
hsa-miR-802	*Homo sapiens*	94	-22.90	CAGUAACAAAGAUUCAUCCUUGU	3′	70

PL: Pre-miRNA length; MFE: Minimal free energy; MS: Mature sequence.

Table 2 Represents the targets of hsa-miR-802-5p based on target scan analysis

Sl. No.	Target gene	Representative transcript	Gene name	Representative miRNA
1	*TMED9*	ENST00000332598.6	Transmembrane emp24 transport domain containing 9	hsa-miR-802
2	*PCNP*	ENST00000296024.5	PEST proteolytic signal containing nuclear protein	hsa-miR-802
3	*C3orf58*	ENST00000441925.2	Chromosome 3 open reading frame 58	hsa-miR-802
4	*NUS1*	ENST00000368494.3	Nuclear undecaprenyl pyrophosphate synthase 1 homolog	hsa-miR-802
5	*ZNF597*	ENST00000301744.4	Zinc finger protein 597	hsa-miR-802

PEST: Proline (P), glutamic acid (E), aspartic acid (D) and serine (S)/threonine (T).

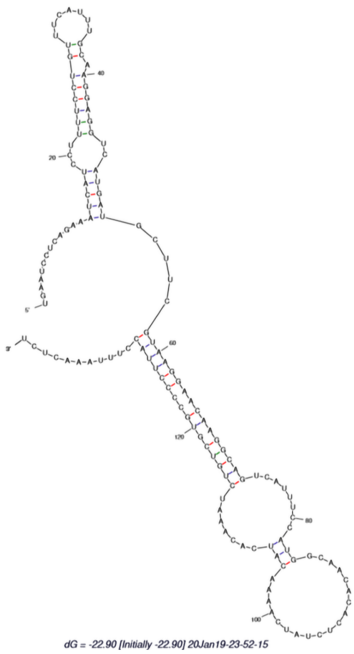

Figure 1 The secondary structure of hsa-miR-802-5p.

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