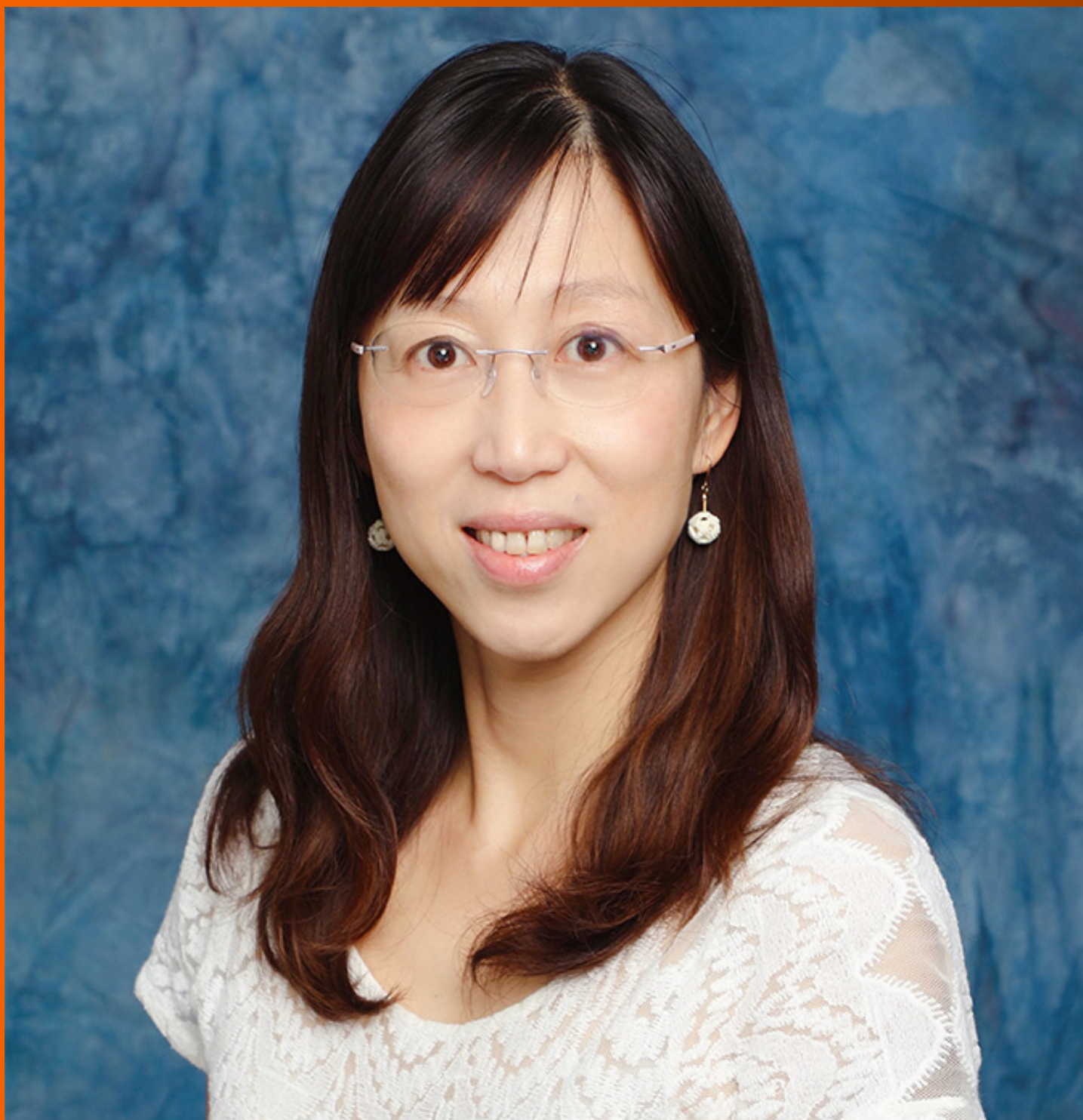


World Journal of *Diabetes*

World J Diabetes 2020 December 15; 11(12): 567-665



FIELD OF VISION

- 567 Identification of miR-802-5p and its involvement in type 2 diabetes mellitus
Rajkumar KV, Lakshmanan G, Sekar D

MINIREVIEWS

- 572 SX-fraction: Promise for novel treatment of type 2 diabetes
Konno S
- 584 Effects of ketogenic diet and ketone bodies on the cardiovascular system: Concentration matters
Nasser S, Vialichka V, Biesiekierska M, Balcerczyk A, Pirola L

ORIGINAL ARTICLE

Basic Study

- 596 Empagliflozin alleviates podocytopathy and enhances glomerular nephrin expression in *db/db* diabetic mice
Klimontov VV, Korbut AI, Taskaeva IS, Bgatova NP, Dashkin MV, Orlov NB, Khotskina AS, Zavyalov EL, Klein T
- 611 Effect of liraglutide on endoplasmic reticulum stress in the renal tissue of type 2 diabetic rats
Zhao XY, Yu TT, Liu S, Liu YJ, Liu JJ, Qin J
- 622 Vanadium-dependent activation of glucose transport in adipocytes by catecholamines is not mediated *via* adrenoceptor stimulation or monoamine oxidase activity
Fontaine J, Tavernier G, Morin N, Carpéné C

Observational Study

- 644 Diabetic patients with COVID-19 need more attention and better glycemic control
Xu M, Yang W, Huang T, Zhou J
- 654 Exenatide once weekly combined with metformin reduced glycemic variability in type 2 diabetes by using flash glucose monitoring system
Li Y, Han MM, He Q, Liu ZA, Liang D, Hou JT, Zhang Y, Liu YF

ABOUT COVER

Editorial board member of *World Journal of Diabetes*, Dr. Luo-Hua Jiang is a biostatistician with a unique combination of expertise in biostatistics, epidemiology, and diabetes research. She obtained her MD degree from Peking University (China) and PhD in Biostatistics from the University of California Los Angeles (United States). She has led a series of investigations examining the relationship of diabetes with mental health and conducted multilevel analysis of the translational effects of lifestyle intervention to prevent diabetes among American Indians and Alaska Natives (AIs/ANs). She has also been funded by the National Institute of Diabetes and Digestive and Kidney Diseases to assess the comparative effectiveness of a diabetes case management intervention in AI/AN communities. She has authored and co-authored more than 80 publications. (L-Editor: Filipodia)

AIMS AND SCOPE

The primary aim of *World Journal of Diabetes* (*WJD*, *World J Diabetes*) is to provide scholars and readers from various fields of diabetes with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJD mainly publishes articles reporting research results and findings obtained in the field of diabetes and covering a wide range of topics including risk factors for diabetes, diabetes complications, experimental diabetes mellitus, gestational diabetes, diabetic angiopathies, diabetic cardiomyopathies, diabetic coma, diabetic ketoacidosis, diabetic nephropathies, diabetic neuropathies, etc..

INDEXING/ABSTRACTING

The *WJD* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, and PubMed Central. The 2020 Edition of Journal Citation Reports® cites the 2019 impact factor (IF) for *WJD* as 3.247; IF without journal self cites: 3.222; Ranking: 70 among 143 journals in endocrinology and metabolism; and Quartile category: Q2.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Yu-Jie Ma; Production Department Director: Xiang Li; Editorial Office Director: Jia-Ping Yan.

NAME OF JOURNAL

World Journal of Diabetes

ISSN

ISSN 1948-9358 (online)

LAUNCH DATE

June 15, 2010

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Timothy Koch

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/1948-9358/editorialboard.htm>

PUBLICATION DATE

December 15, 2020

COPYRIGHT

© 2020 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



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

Kaushik Vishnu Rajkumar, Ganesh Lakshmanan, Durairaj Sekar

ORCID number: Kaushik Vishnu Rajkumar [0000-0002-2502-088X](https://orcid.org/0000-0002-2502-088X); Ganesh Lakshmanan [0000-0002-6078-2900](https://orcid.org/0000-0002-6078-2900); Durairaj Sekar [0000-0002-0722-8636](https://orcid.org/0000-0002-0722-8636).

Author contributions: Rajkumar KV completed the experimental work and execution; Lakshmanan G finished manuscript corrections and results analysis; and Sekar D completed manuscript writing, experimental work and data analysis.

Conflict-of-interest statement: There is no conflict of interest.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Specialty type: Endocrinology and

Kaushik Vishnu Rajkumar, Ganesh Lakshmanan, Department of Anatomy, Saveetha Dental College and Hospital, Saveetha Institute of Medical and Technical Science (SIMATS), Saveetha University, Chennai 600077, India

Durairaj Sekar, Dental Research Cell and Biomedical Research Unit (DRC-BRULAC), Saveetha Dental College and Hospital, Saveetha Institute of Medical and Technical Science (SIMATS), Saveetha University, Chennai 600077, India

Corresponding author: Durairaj Sekar, PhD, Professor, Dental Research Cell and Biomedical Research Unit (DRC-BRULAC), Saveetha Dental College and Hospital, Saveetha Institute of Medical and Technical Science (SIMATS), Saveetha University, 162, Poonamallee High Rd, Velappanchavadi, Chennai 600077, India. duraimku@gmail.com

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 complementarity. 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

©The Author(s) 2020. Published by Baishideng Publishing Group Inc. All rights reserved.

metabolism

Country/Territory of origin: India**Peer-review report's scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0

Received: June 26, 2020**Peer-review started:** June 26, 2020**First decision:** September 24, 2020**Revised:** October 3, 2020**Accepted:** October 29, 2020**Article in press:** October 29, 2020**Published online:** December 15, 2020**P-Reviewer:** Zhang LL**S-Editor:** Gao CC**L-Editor:** Filipodia**P-Editor:** Ma YJ

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.

Citation: Rajkumar KV, Lakshmanan G, Sekar D. Identification of miR-802-5p and its involvement in type 2 diabetes mellitus. *World J Diabetes* 2020; 11(12): 567-571

URL: <https://www.wjgnet.com/1948-9358/full/v11/i12/567.htm>

DOI: <https://dx.doi.org/10.4239/wjd.v11.i12.567>

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 complementarity. 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.albany.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	<i>Homo sapiens</i>	94	-22.90	CAGUACAAAGAUUCAUCCUUGU	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	<i>TMED9</i>	ENST00000332598.6	Transmembrane emp24 transport domain containing 9	hsa-miR-802
2	<i>PCNP</i>	ENST00000296024.5	PEST proteolytic signal containing nuclear protein	hsa-miR-802
3	<i>C3orf58</i>	ENST00000441925.2	Chromosome 3 open reading frame 58	hsa-miR-802
4	<i>NUS1</i>	ENST00000368494.3	Nuclear undecaprenyl pyrophosphate synthase 1 homolog	hsa-miR-802
5	<i>ZNF597</i>	ENST00000301744.4	Zinc finger protein 597	hsa-miR-802

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

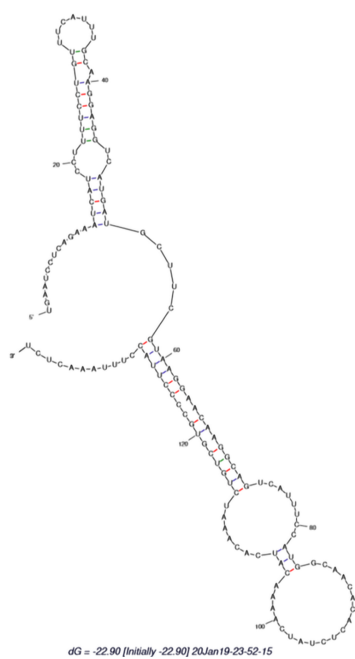


Figure 1 The secondary structure of hsa-miR-802-5p.

REFERENCES

1 **Cheng Z**, Li Z, Ma K, Li X, Tian N, Duan J, Xiao X, Wang Y. Long Non-coding RNA XIST Promotes Glioma Tumorigenicity and Angiogenesis by Acting as a Molecular Sponge of miR-429. *J Cancer* 2017; **8**: 4106-4116 [PMID: 29187887 DOI: 10.7150/jca.21024]

2 **O'Connell RM**, Rao DS, Chaudhuri AA, Baltimore D. Physiological and pathological roles for microRNAs in the immune system. *Nat Rev Immunol* 2010; **10**: 111-122 [PMID: 20098459 DOI: 10.1038/nri2708]

3 **Zen K**, Zhang CY. Circulating microRNAs: a novel class of biomarkers to diagnose and monitor human cancers. *Med Res Rev* 2012; **32**: 326-348 [PMID: 22383180 DOI: 10.1002/med.20215]

4 **Gennarino VA**, D'Angelo G, Dharmalingam G, Fernandez S, Russolillo G, Sanges R, Mutarelli M, Belcastro V, Ballabio A, Verde P, Sardiello M, Banfi S. Identification of microRNA-regulated gene networks by expression analysis of target genes. *Genome Res* 2012; **22**: 1163-1172 [PMID: 22345618 DOI: 10.1101/gr.130435.111]

5 **Dweep H**, Sticht C, Pandey P, Gretz N. miRWalk--database: prediction of possible miRNA binding sites by "walking" the genes of three genomes. *J Biomed Inform* 2011; **44**: 839-847 [PMID: 21605702]

DOI: [10.1016/j.jbi.2011.05.002](https://doi.org/10.1016/j.jbi.2011.05.002)]

- 6 **Thanabalasingham G**, Pal A, Selwood MP, Dudley C, Fisher K, Bingley PJ, Ellard S, Farmer AJ, McCarthy ML, Owen KR. Systematic assessment of etiology in adults with a clinical diagnosis of young-onset type 2 diabetes is a successful strategy for identifying maturity-onset diabetes of the young. *Diabetes Care* 2012; **35**: 1206-1212 [PMID: [22432108](https://pubmed.ncbi.nlm.nih.gov/22432108/) DOI: [10.2337/dc11-1243](https://doi.org/10.2337/dc11-1243)]
- 7 **Nanditha A**, Ma RC, Ramachandran A, Snehalatha C, Chan JC, Chia KS, Shaw JE, Zimmet PZ. Diabetes in Asia and the Pacific: Implications for the Global Epidemic. *Diabetes Care* 2016; **39**: 472-485 [PMID: [26908931](https://pubmed.ncbi.nlm.nih.gov/26908931/) DOI: [10.2337/dc15-1536](https://doi.org/10.2337/dc15-1536)]
- 8 **Chawla A**, Chawla R, Jaggi S. Microvascular and macrovascular complications in diabetes mellitus: Distinct or continuum? *Indian J Endocrinol Metab* 2016; **20**: 546-551 [PMID: [27366724](https://pubmed.ncbi.nlm.nih.gov/27366724/) DOI: [10.4103/2230-8210.183480](https://doi.org/10.4103/2230-8210.183480)]
- 9 **Veazie S**, Winchell K, Gilbert J, Paynter R, Ivlev I, Eden KB, Nussbaum K, Weiskopf N, Guise JM, Helfand M. Rapid Evidence Review of Mobile Applications for Self-management of Diabetes. *J Gen Intern Med* 2018; **33**: 1167-1176 [PMID: [29740786](https://pubmed.ncbi.nlm.nih.gov/29740786/) DOI: [10.1007/s11606-018-4410-1](https://doi.org/10.1007/s11606-018-4410-1)]
- 10 **Shi CY**, Yang H, Wei CL, Yu O, Zhang ZZ, Jiang CJ, Sun J, Li YY, Chen Q, Xia T, Wan XC. Deep sequencing of the Camellia sinensis transcriptome revealed candidate genes for major metabolic pathways of tea-specific compounds. *BMC Genomics* 2011; **12**: 131 [PMID: [21356090](https://pubmed.ncbi.nlm.nih.gov/21356090/) DOI: [10.1186/1471-2164-12-131](https://doi.org/10.1186/1471-2164-12-131)]
- 11 **Priyanka P**, Panagal M, Sivakumar P, Gopinath V, Ananthavalli R, Karthigeyan M, Paramasivam S, SR SK, Sekar D. Identification, expression, and methylation of miR-7110 and its involvement in type 1 diabetes mellitus. *Gene Rep* 2018; **11**: 229-234 [DOI: [10.1016/j.genrep.2018.03.015](https://doi.org/10.1016/j.genrep.2018.03.015)]
- 12 **Bai L**, Li J, Panagal M, M B, Sekar D. Methylation dependent microRNA 1285-5p and sterol carrier proteins 2 in type 2 diabetes mellitus. *Artif Cells Nanomed Biotechnol* 2019; **47**: 3417-3422 [PMID: [31407919](https://pubmed.ncbi.nlm.nih.gov/31407919/) DOI: [10.1080/21691401.2019.1652625](https://doi.org/10.1080/21691401.2019.1652625)]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Telephone: +1-925-3991568

E-mail: bpgoffice@wjgnet.com

Help Desk: <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

