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CircHIPK3, and has_circ_0071106 as biomarkers for diabetes among first degree relatives of type 2 diabetes patients

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ABSTRACT

Background: Most patients in Egypt with prediabetes and 43% of those with diabetes are probably undiagnosed. So early detection of T2D is of utmost importance to prevent progression to irreversible complications. Many of the biomarkers used today for detection of diabetes are based on proteins. The discovery of circular RNA as a sensitive, and non-invasive biomarker opened new frontiers for diagnosis, prognosis, and therapeutic response prediction of diseases including diabetes. The aim of this study was to evaluate the potential of CircHIPK3 and hsa_circ_0071106 as diagnostic biomarkers for prediabetes in apparently healthy first-degree relatives of patients with T2D. Methods: This study is of case-control design. It includes 78 subjects distributed equally between cases and control groups. Glycemic profile parameters including (fasting and 2 hrs plasma glucose during oral glucose tolerance test, HbA1c, and insulin) in addition to calculation of Insulin resistance's homeostasis model assessment parameter (HOMA-IR) were performed. Expression level of CircHIPK3, and hsa_circ_0071106 was quantified using Quantitative real-time polymerase chain reaction (RT-qPCR). Results: In the relative's group, subjects who had diabetes showed significantly higher levels of both CircHIPK3 and hsa_circ_0071106 in comparison to others that are either euglycemic or prediabetic ($P<0.001$, and $P=0.003$, respectively). The accuracy of the differentiation between T2DM patients and control subjects was comparable for CircHIPK3 and hsa_circ_0071106 (93.3%, and 96.7% respectively). Conclusions: Elevated levels of CircHIPK3 and hsa_circ_0071106 were significantly associated with the presence and progression of glucose impairment in 1st degree relatives of T2D. Specifically, CircHIPK3 seems to be an independent predictor of prediabetes.

Introduction

Diabetes, a metabolic disease characterized by high blood glucose and other consequences. Its causes are unknown, and there are several risk factors, such as poor diet, unhealthy lifestyles, and genetic predisposition. Because of metabolic

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dysfunction, individuals with type 2 diabetes (T2D) exhibit a relative insulin deficiency[1].

In 2021, according to The International Diabetes Federation (IDF), Egypt has the tenth-highest number of T2D patients worldwide with expectation to jump to the ninth rank by 2045. In Egypt, the prevalence of diabetes is around 15.56% among adults between 20 and 79 years of age, and the condition causes 86,478 deaths annually [2].

Additionally, estimates show that the majority of patients in Egypt with prediabetes and 43% of those with diabetes are probably undiagnosed. Over the past 20 years, the prevalence of type 2 diabetes in Egypt has nearly tripled. This dramatic increase may be due to various risk factors specific to Egypt or to an increase in the usual risk factors for type 2 diabetes, such as obesity, physical inactivity, and dietary changes. These include a higher incidence of chronic hepatitis C and more exposure to environmental risk factors like pesticides [3,4].

The American Diabetic association set the criteria for diagnosis of diabetes based on level of blood glucose and/or HbA1c concentration. It is highly beneficial to detect diabetes mellitus early in order to stop developing and worsening of complications [5].

Many indicators of diabetes mellitus have been found, such as urinary 8-oxo-7,8-dihydro-2-deoxyguanosine, serum adipocyte fatty acid–binding protein, 2-aminoadipic acid, GDF-15, and YKL-40. Non-coding RNAs (ncRNAs) have emerged as a new sensitive, noninvasive biomarker for diagnosis, prognosis, and therapeutic response prediction in recent years due to their high stability in bodily fluids (plasma, urine, etc.) and the development of new detection techniques, even though many of the biomarkers used today are based on proteins [6].

It has been discovered that non-coding RNAs (ncRNAs), a class of RNAs with minimal transcriptional value, play a significant role in post-transcriptional and epigenetic regulation of gene expression, including messenger RNA (mRNA) silencing. They may be broadly divided, based upon their size, into small ncRNAs and long ncRNAs (LncRNA) [7].

One subclass of LncRNA is circular RNA (CircRNAs). They are produced from precursor mRNAs but lack the 5'Cap and polyA tail and have a covalently closed loop structure. The biological functions exerted by CircRNA are highly diverse. They can function as protein sponges and steadily control the activity of RNA-binding protein (RBP) or as effective and persistent microRNA (miRNA) inhibitor and control the expression levels of the target genes[8].

Numerous circRNAs have been shown to regulate autophagy, immunological inflammation, and cellular dysfunction in diabetes. The circular RNA homeodomain-interacting protein kinase 3 (CircHIPK3), also known as hsa_circ_0000284, has been shown to be prevalent in pancreatic islets and has a role in insulin resistance and hyperglycemia. CircHIPK3 can specifically up-regulate FOXO1 and sponge miR-192-5p, which can affect glucose homeostasis. Studies have demonstrated that the diagnostic value of hsa_circ_0071106 for type 2 diabetes is acceptable, as it can distinguish between patients and healthy controls [9].

As the early detection of T2D is of utmost importance to prevent progression to irreversible complications, and based on previous literature [9–11], we aimed from this study to evaluate the potential of CircHIPK3 and hsa_circ_0071106 as diagnostic biomarkers for prediabetes in apparently healthy 1st degree relatives of patients with T2D.

Methods:

Study design and subjects:

This study is of a case-control design, which was carried out between April 2024 to May 2025. The sample size was calculated by assuming the expression of hsa_circ_0071106 was 1.19 ±0.36 vs 1.002±0.2 in diabetic patient vs control [12]. At 80% power and 95 % CI, the estimated sample will be 78 subjects, 39 subjects in each group (Open Epi). Epi Info Software (Atlanta, Georgia, USA) was used for calculating the sample size**.** The study proposal gained approval from Zagazig University Institutional Review Board (ZU-IRB#156/5-March-2024). Written informed consent was secured from every participant in accordance with the 1979 Declaration of Helsinki.

We designated participants based on our inclusion criteria (i.e., approval for enrollment in study, first-degree relatives of T2D patients [parents, siblings, offsprings] who are more than or equal 18 years old and were not previously diagnosed as diabetics). Subjects refusing to participate in the study, subject's age is less than 18 years old, far relatives of T2D patients and relatives of cases with other types of diabetes and diagnosed

cases of diabetes, malignancy or any chronic inflammatory condition were excluded from this study. The participants were selected by simple random sampling. Everyone underwent a comprehensive clinical history review and clinical evaluation.

Sample collection and routine biochemical tests:

The sampling of blood into 3 types of vacutainers (fluoride/oxalate tubes, EDTA tube and plain tubes) was performed. Laboratory investigations included fasting and 2 hrs plasma glucose during oral glucose tolerance test (OGTT). Fluoride/oxalate vacutainers were used to separate plasma for measurement of these tests that was performed on Cobas c702/8000 (Roche diagnostic, Mannheim, Germany). Whole blood (from EDTA tube) was used to measure HbA1C on Cobas c502/6000 (Roche diagnostic, Mannheim, Germany). Tests procedures, interpretation of results and later categorization of case group into euglycemic (25 participant), impaired glucose tolerance /prediabetic-as a short term- (9 participant) and diabetics (5 participant) depended on ADA standards of medical care in diabetes guidelines [5] and WHO criteria for interpreting 2-h OGTT [13]. Any participant that was destined to be in the control group but fulfilled the ADA criteria, was excluded from the study, advice to see an endocrinologist for follow up and replaced with another candidate. In total, 7 candidates were excluded.

Serum separated from plain vacutainers was used to measure insulin level using the Human Insulin ELISA kit (Cat. No.: 201-12-0011) (SunRed Biotechnology, Shanghi, China) and another serum aliquot was utilized to extract RNA. Insulin resistance's homeostasis model assessment parameter (HOMA-IR) was computed [14].

Quantitative real-time PCR for CircHIPK3, and hsa_circ_0071106:

Expression level of CircHIPK3, and hsa_circ_0071106 was quantified using Quantitative real-time polymerase chain reaction (RT-qPCR). RNA was extracted from serum using the miRNeasy Serum/Plasma kit (Qiagen, Hilden, Germany). The procedures were carried out according to the guidelines provided by the manufacturer. The RNA was evaluated using gel electrophoresis and a spectrophotometer (Nano Drop 1000, Wilmington, DE, USA). The miScript RT II kit from QIAGEN GmbH in Hilden, Germany, uses one microgram of extracted RNA to carry out the reverse transcription procedure. The miScript SYBR Green PCR Kit (Qiagen, Germany) and the StepOneTM System (Applied Biosystems, USA) were used to amplify up the cDNA. All procedures followed the guidelines provided by the manufacturer. The following is how the real-time cycler is configured: At 95 °C, the first denaturation was supposed to take place in 15 minutes. An annealing step at 58 °C for 30 seconds, followed by extension at 70 °C for 30 seconds, and a denaturation step at 95 °C for 15 seconds were all part of the forty cycles that the thermal process was designed to run through.

Primers sequences of the tested cirRNA and GAPDH (internal control) are as mentioned in Table (1).

Every sample's CT was determined using the amplification curves. To evaluate the amplified product's specificity, melting curve analysis was used (supplementary figure 1). The fold change was calculated with the help of $2^{-\Delta\Delta Ct}$ [15].

Statistical analysis:

Post-Hoc Dunn's test was employed after Kruskal-Wallis for data comparison in quantitative variables. For qualitative data, the Chi square test was used. A Spearman correlation analysis was done to look at the connection between the marker and clinical variables. An analysis of the receiver operating characteristic (ROC) curve was used to assess the diagnostic performance. The predicted factors were found through the application of both univariate and multivariate analysis. Less than 0.05 values indicated statistical significance. SPSS 26 was used to analyze data (Chicago, IL, USA).

Results:

Table 2 displays the demographic and laboratory data of the study participants. Age (P = 0.16) and gender (P = 0.64) did not significantly differ between groups under study. According to our findings, T2DM patients' glycemic profile values were significantly higher than those of euglycemic, prediabetes, and controls. Additionally, glycemic profile was higher in prediabetes when compared to controls.

In the relative's group, subjects who had diabetes showed significantly higher levels of both CircHIPK3 and hsa_circ_0071106 in comparison to others that are either euglycemic or prediabetic (P<0.001, and P=0.003, respectively). Figure 1 illustrates the expressions CircHIPK3 and hsa_circ_0071106. The prediabetes group exhibited significantly increased expression of the two

selected circular RNAs compared to the euglycemic group (P<0.001 and P< 0.001 respectively). Whereas, when comparing T2DM and prediabetes groups, T2DM group showed significantly increased expression of CircHIPK3 (P=0.042). A ROC curve analysis was carried out and is displayed in Figure 2 to ascertain the diagnostic values of selected circular RNAs for glucose impairment and T2DM. Table 3 displayed the AUCs and performance characteristics of studied circular RNAs in the prediction of T2DM versus control, T2DM versus prediabetes, and prediabetes versus control. The accuracy of the differentiation between T2DM patients and control subjects was comparable for CircHIPK3 and hsa_circ_0071106 (93.3%, and 96.7% respectively). Furthermore, in T2DM vs prediabetes, hsa_circ_0071106 maintains good sensitivity (80%) and perfect specificity (100%), whereas CircHIPK3 shows moderate sensitivity (60%) and perfect specificity.

The association of clinical parameters and circular RNAs were examined using Spearman correlation analysis. The findings showed a statistically significant positive correlation was found between the glycemic profile parameters and the circular RNAs examined as shown in Table 4. Additionally, a significant positive correlation exists between CircHIPK3 and hsa_circ_0071106 (r=0.33, P =0.003).

Logistic regression analysis of prediction of pre-diabetes from euglycemic was assessed in Table 5. The univariate logistic regression showed that CircHIPK3 and hsa_circ_0071106 were risk factors. A multivariate logistic regression analysis was conducted to identify factors associated with prediabetes. Elevated levels of CircHIPK3 were significantly linked to an increased risk of prediabetes. Specifically, each unit increase in CircHIPK3 expression was associated with an approximately 82.9-fold rise in the odds of developing prediabetes.

Table 1: Primers of the markers studied

Target	Forward primer	Reverse primer
CircHIPK3	5’ TGG AGA CTG GGG GAA GAT GA’3	5’CAC ACT AAC TGG CTG AGG GG’3
hsa_circ_0071106	5’GAAGCTGCTGATCGGAAGAAA’3	5’GCCGGTTCTGCTCTACTTGG’3
GAPDH	5’GCACCGTCAAGGCTGAGAAC’3	5’ TGGTGAAGACGCCAGTGGA’3

Table 2: Demographic and laboratory data of the studied participants

Parameter	Controls (No.= 39)	Relatives (No.= 39)			p
		Euglycemic (No. =25)	Pre-diabetes (No.=9)	T2DM patients (No. = 5)	
Age (years)	48 [37-55]	45.5 [37.5-55]	45.5 [37-62]	45 [37-52]	0.16
Sex: Male/ Female	31/8 (79.5/20.5)	19/6 (76/24)	8/1 (88.9/11.1)	3/2 (60/40)	0.64
BMI (Kg/m2)	26.3 [24.5-28.1]	26.4 [24.8-27.3]	26.4 [23.3-27]	26.1 [24.7-27.2]	0.96
Fasting glucose (mg/dL)	84 [70-93] [b, c]	85.5 [70-93] [b, c]	119 [108-125] [a, c]	280 [180-363] [a, b]	<0.001*
2h postprandial glucose (mg/dL)	120 [105-138] [b, c]	118.2 [105-128] [b, c]	153 [145-185] [a, c]	322 [222-405] [a, b]	<0.001*
Insulin (µU/L)	9.2 [6-12.2] [b, c]	8.6 [6.2-12.2] [b, c]	14.3 [12.2-18] [a, c]	21.2 [15.2-25] [a, b]	<0.001*
HOMA IR	1.8 [1.2-2.5] [b, c]	1.7 [1.2-2.6] [b, c]	4.3 [3.3-5] [a, c]	12.4 [6.8-19.6] [a, b]	<0.001*
HbA1c (%)	5 [4.3-5.4] [b, c]	5.1 [4.3-5.5] [b, c]	6.1 [5.7-6.4] [a, c]	8.6 [7-9.2] [a, b]	<0.001*

T2DM: Type 2 diabetes mellites; BMI: Body mass index; HOMA-IR: Homeostatic model assessment for insulin resistance; HbA_1c: Hemoglobin A_1c.
Data are presented as median [range]
p= Kruskal-Wallis followed by Hoc Dunn's test; a: difference in comparison to euglycemic; b: difference in comparison to prediabetes*; c: difference in comparison to T2DM*
* Significant

Table 3: Diagnostic performance characteristics of studied markers

Marker	AUC [95% CI]	Cutoff (fold change)	Youden's index	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
T2DM vs controls								
CircHIPK3	0.964 [0.891-1.037]	≥ 1.15	0.76	80	96	80	96	93.3
hsa_circ_0071106	0.996 [0.980-1.012]	≥ 1.35	0.96	100	96	83.3	100	96.7
T2DM vs prediabetes								
CircHIPK3	0.678 [0.313-1.043]	≥ 3.05	0.60	60	100	100	81.8	85.7
hsa_circ_0071106	0.844 [0.562-1.127]	≥ 3.1	0.80	80	100	100	90	92.9
Prediabetes vs controls								
CircHIPK3	0.962 [0.902-1.022]	≥ 1.15	0.74	77.8	96	87.5	92.3	91.2
hsa_circ_0071106	0.982 [0.946-1.018]	≥ 1.3	0.84	88.9	96	88.9	96	94.1

AUC: Area under the ROC curve; CI: Confidence interval; PPV: Positive predictive value; NPV: Negative predictive value; T2DM: Type 2 diabetes mellites.

Table 4: Correlation results of studied markers with other parameters

Parameter	CircHIPK3		hsa_circ_0071106	
	r	p	r	p
Age	-0.19	0.09	0.01	0.99
BMI	-0.03	0.79	0.12	0.29
Fasting Glucose	0.53	<0.001*	0.48	<0.001*
2h postprandial glucose	0.43	<0.001*	0.46	<0.001*
Insulin	0.52	<0.001*	0.25	0.029*
HOMA IR	0.54	<0.001*	0.29	0.008*
HbA1c	0.51	<0.001*	0.22	0.056
CircHIPK3	1	-------	0.33	0.003*
hsa_circ_0071106	0.33	0.003*	1	------

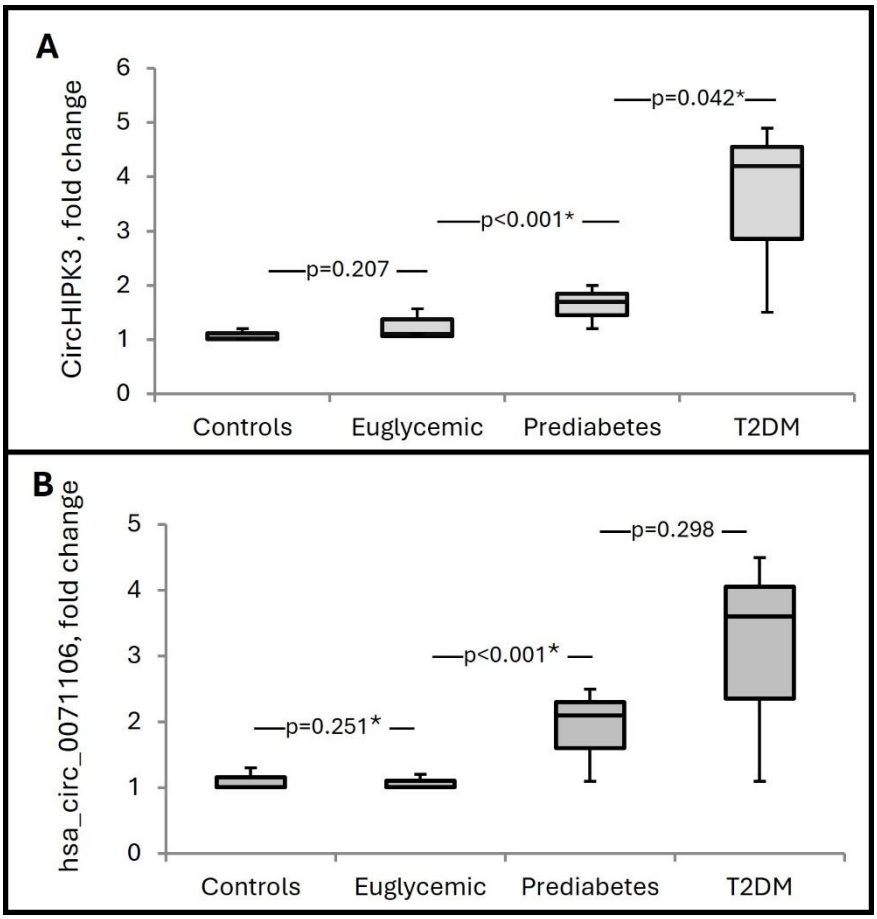
BMI: Body mass index; HOMA-IR: Homeostatic model assessment for insulin resistance; HbA_1c: Hemoglobin A_1c.
**: Significant*

Table 4: Correlation results of studied markers with other parameters

Parameter	CircHIPK3		hsa_circ_0071106	
	r	p	r	p
Age	-0.19	0.09	0.01	0.99
BMI	-0.03	0.79	0.12	0.29
Fasting Glucose	0.53	<0.001*	0.48	<0.001*
2h postprandial glucose	0.43	<0.001*	0.46	<0.001*
Insulin	0.52	<0.001*	0.25	0.029*
HOMA IR	0.54	<0.001*	0.29	0.008*
HbA1c	0.51	<0.001*	0.22	0.056
CircHIPK3	1	-------	0.33	0.003*
hsa_circ_0071106	0.33	0.003*	1	------

BMI: Body mass index; HOMA-IR: Homeostatic model assessment for insulin resistance; HbA_1c: Hemoglobin A_1c.: Significant*

Figure 1: Levels of (A) CircHIPK3 and (B) hsa_circ_0071106 in study subjects.



Supplementary figure (1): Melting curves of the studied markers (A): hsa_circ_0071106, (B): CircHIPK3.

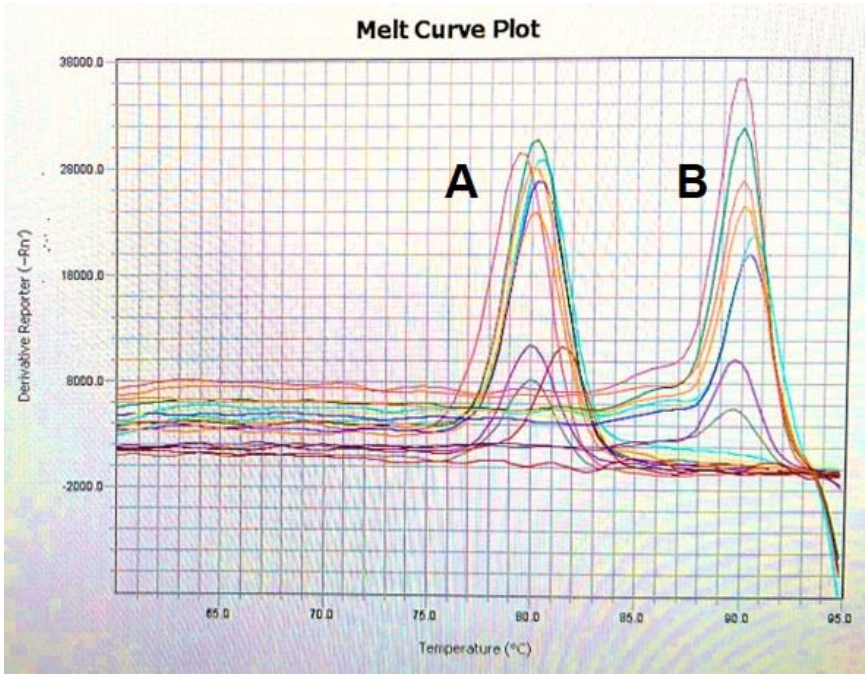
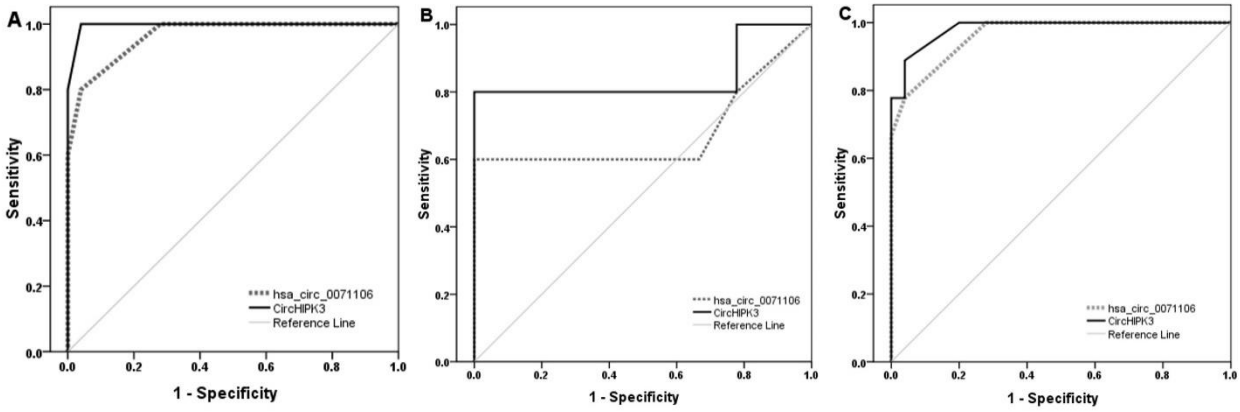


Figure 2: ROC curves of markers in glucose impairment prediction in the relatives (A) T2DM vs. euglycemic, (B) T2DM vs. prediabetes, and (C) Prediabetes vs. euglycemic



Discussion

In diabetes, many circRNAs, among which are CircHIPK3, and hsa_circ_0071106, were linked to regulation of immune inflammation, and autophagy [9]. CircHIPK3 was found to be essential for the maintenance of normal β-cell functions. Silencing of CircHIPK3 in rat's islet cells resulted in increased apoptosis, decreased proliferative capacity of the cells, and impaired insulin secretion in response to glucose. These actions are mainly mediated via miRNA sponging (i.e., miR-124-3p, miR-29-3p, miR-338-3p, and miR-30) [9,16]. However, additional biological processes like as protein binding, gene transcription regulation, or the Mitogen-activated protein kinase (MAPK) signaling pathway, which controls insulin signal transduction, have been linked to hsa_circ_0071106 [10].

The purpose of the current study was to investigate the potential use of hsa_circ_0071106 and CircHIPK3 as biomarkers for diabetes detection in 1st degree relatives of T2D patients.

Based on our selection criteria and ADA criteria for diagnosis of diabetes, 14 participants (9 prediabetics and 5 diabetics) were detected among 1st degree relatives of T2D patients. This represents 35.9% of the studied sample, a result approaching that reported previously about the percentage of undetected cases of diabetes (43%) among Egyptian population [3]. In a more recent study, prevalence of diabetes was 40% of the studied population [17]. This high prevalence makes it a must for early detection and so management of diabetes to prevent the expected complications.

Our study for the expression level of CircHIPK3 in peripheral blood of 1st relatives of T2DM patients, showed that it had a higher expression in affected individuals (diabetics or prediabetics) while their expression was comparable between the euglycemic and the control group. Also, it had a higher expression in diabetic than prediabetic groups. As its expression gradually increased from euglycemic (control or 1st degree relatives) to prediabetic to diabetic individuals, we could suggest its possible use as predictor/diagnostic marker for T2DM. Interestingly, studies for CircHIPK3 expression level in hyperglycemia-induced complications showed that its level is increased in both micro and macrovascular complications, whereas, its decreased level promotes diabetic cardiomyopathy by stimulating cell apoptosis [18]. At ≥ 3.05 cutoff, it has 60% sensitivity, 100% specificity, and 85.7% accuracy in differentiating T2DM from prediabetic individuals with 0.6 as the highest Youden's index.

Also, ≥ 1.15 cutoff, it has 77.8% sensitivity, 96% specificity, and 91.2% accuracy in differentiating prediabetic from control individuals with 0.74 as the highest Youden's index. Previous reports showed similar results with CircHIPK3 expression level higher in T2DM than control individuals (P<0.001) and prediabetic ones (P=0.0180). They reported using a cutoff of 0.25 to differentiate T2DM patients from the pre-diabetes (sensitivity and specificity of 50% and 75% respectively) [11]. Meanwhile, other study didn't prove the same result reporting that CircHIPK3 expression level was not statistically significantly different between diabetic and control group [10]. There are some reasons for the conflicting results of the levels of CircHIPK3 expression in diabetes and control groups. Results can be greatly impacted by variations in study design, including variations in population demographics, including inclusion

criteria such as ethnicity, age distribution, genetic variety, and treatment status.

CircHIPK3 expression level was positively correlated with diabetes indicators (i.e. fasting and 2 hrs. postprandial glucose, insulin level, HOMA IR, and HbA1c) and with hsa_circ_0071106 expression level. In agreement with our results, Rezaeinejad and coworkers showed the same correlation with diabetes indicators in addition to positive correlation with systolic blood pressure and body mass index [11]. Su and coworkers reported its positive correlation with fasting blood glucose and lipid parameters (i.e. total cholesterol, triglycerides, LDL and HDL) [12].

The expression level of hsa_circ_0071106, as well, was higher in affected individuals' peripheral blood vs the non-affected ones. So, we assumed its value as a diagnostic biomarker for T2DM. However, as the expression level of hsa_circ_0071106 didn't differ between prediabetics and diabetics individuals, we could not assume that it could be used to mark the transition of individual from the former to the later stage.

Previous studies of hsa_circ_0071106 in T2DM patients found that, in agreement with our results, hsa_circ_0071106 has higher expression in diabetic patients, both as a single marker [10] or when combined with other circular RNAs [12]. Our study of the diagnostic value of hsa_circ_0071106 for type 2 diabetes using ROC analysis showed that at cutoff ≥1.35, AUC was 0.996, sensitivity was 100% and specificity was 96%. Previously, AUC, as low as 0.563, was reported by Su and coworkers [12]. Yingying and coworkers reported AUC of 0.587, 82.5% sensitivity and 35.9% specificity as diagnostic values for T2DM [10]. hsa_circ_0071106 expression level was positively correlated with diabetes indicators (i.e. fasting and 2 hrs. postprandial glucose, insulin level, and HOMA IR) and with CircHIPK3 expression level. The same positive correlation with fasting blood glucose was noted by Su and coworkers [12]. Overall, these findings suggest that both circHIPK3 and hsa_circ_0071106 are associated with key markers of glucose metabolism and insulin resistance and may serve as potential biomarkers or contributors to the pathophysiology of glucose dysregulation.

CircHIPK3 appears to be an independent predictor of the prediabetes, with significant associations maintained after adjusting for potential confounders. But, when controlling for other factors, hsa_circ_0071106's association with the outcome is less clear or possibly confounded. These results are in agreement with Akella et al. [19] who found that altered expression of circHIPK3 may be involved in the onset of diabetes mellitus.

The present study has certain limitations. First, although the sample size is statistically adequate, it is relatively small, and a larger sample may yield clearer results. Second, as a case-control design, the study does not involve follow-up of the participants, which limits the ability to assess temporal relationships or determine the predictive potential of the findings for future complications. Lastly, the study did not explore the underlying biological mechanisms linking these circular RNAs to glucose metabolism, which would be valuable for understanding their role in disease progression and potential therapeutic targets.

Conclusion:

Elevated levels of CircHIPK3 and hsa_circ_0071106 were significantly associated with the presence and progression of glucose impairment in 1st degree relatives of T2D. The high diagnostic accuracy of these circular RNAs emphasizes their potential as reliable biomarkers for early detection and risk stratification of individuals at high risk of developing T2D. Specifically, CircHIPK3 seems to be an independent predictor of prediabetes.

Conflict of Interest:

Non declared.

Financial Disclosures:

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