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Expression and diagnostic value of lncRNA HCG18 in gestational diabetes mellitus

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ABSTRACT

Objectives: Gestational diabetes mellitus (GDM) is the first type of diabetes induced by abnormal maternal glucose metabolism after pregnancy. Long non-coding RNA (lncRNA) has been found to be of great value in the study of its pathogenesis and treatment. This study aimed to explore the expression and diagnostic value of lncRNA HCG18 in GDM.

Material and methods: The expression levels of HCG18 in serum of participating GDM patients and healthy controls were detected by polymerase chain reaction (RT-qPCR). The correlation between the expression of HCG18 and the blood glucose level was clarified by the detection of blood glucose levels in GDM patients. The receiver operating characteristic curve (ROC) was used to evaluate the clinical diagnostic value of HCG18 for GDM. Furthermore, multivariate logistic analysis was used to verify the diagnostic value of HCG18 in GDM.

Results: This study concluded that the expression level of HCG18 was upregulated in the serum of GDM patients compared with the control group. ROC curve showed that the AUC was 0.916, the sensitivity was 80.5%, the specificity was 90.2%, and multivariate logistic regression analysis verified that HCG18 (OR = 6.984, 95% CI = 3.751–13.005, $p < 0.001$) was significantly associated with GDM, which suggesting that HCG18 has diagnostic significance for GDM. In addition, the expression of HCG18 was positively correlated with fasting blood glucose, 1h blood glucose and 2 h blood glucose of patients.

Conclusions: LncRNA HCG18 was elevated in patient serum and might serve as a diagnostic biomarker for GDM.

Keywords: lncRNA HCG18; gestational diabetes mellitus; blood glucose; diagnostic

INTRODUCTION

Gestational diabetes mellitus (GDM) is the first diagnosed during pregnancy in patients with normal glucose metabolism or latent hypoglycemia before pregnancy [1]. Data show that GDM accounts for 80 percent of all diabetes-related pregnant women [2]. Gestational diabetes mellitus may cause maternal infection, increased amniotic fluid, fetal hyperglycemia, excessive insulin secretion, and complications such as hypertension and neonatal hypoglycemia [3–5]. The prevalence of GDM has increased significantly in recent years, due to changes in lifestyle and personal dietary habits. Currently, dietary therapy and drug therapy are the main treatment methods. Reasonable dietary control not only needs to ensure basic energy needs, but also avoid postprandial hyperglycemia or starvation ketosis to ensure the normal growth and development of the fetus [4]. If the blood sugar level cannot be effectively controlled in a short period of time, insulin therapy needs to be added according to the specific condition of the pregnant woman [6]. Therefore, it is necessary to explore new ways to detect and diagnose GDM in time.

LncRNAs have been found to act as biotherapeutic and prognostic targets in many diseases. For example, lncRNA SNHG5 can be used as a molecular therapeutic target for patients with various novel cancers [7] , as well as MIR22HG [8]. LncRNA HLA complex group 18 (HCG18) belongs to the HLA complex group [9], HCG18 played an oncogenic role in osteosarcoma via miR-148b/ETV5, promoting osteosarcoma cell proliferation and metastasis in previous studies [10]. Exosome-mediated HCG18 promoted the polarization of M2 macrophages in gastric cancer by decreasing miR-875-3p in macrophages [11]. In addition, HCG18 has also been demonstrated to have regulatory ability in diabetic peripheral neuropathy, cardiovascular disease [12], that expect to clear cell renal cell carcinoma [13], hepatocellular carcinoma [14], and nasopharyngeal carcinoma [15]. However, the role of HCG18 in GDM remains unclear and requires in-depth exploration.

The current study aims to explore the expression and diagnostic value of HCG18 in GDM, to understand the potential of HCG18 as a diagnostic biomarker for GDM, and to provide theoretical reference for the subsequent treatment of GDM patients.

MATERIAL AND METHODS

Information of participants

The clinical sample was 230 participants from Central Hospital of Enshi Tujia and

Miao Autonomous Prefecture, including GDM patients (n = 118) and controls (n = 112). Referring to the Chinese diagnostic criteria of GDM, fasting blood glucose at 5.1 mmol/L, 1 hour after taking glucose at 10.0 mmol/L, and 2 hours after taking glucose at 8.5 mmol/L were taken as the critical blood glucose. Gestational diabetes mellitus was diagnosed when the fasting blood glucose level or the blood glucose level diagnosed by 75 g OGTT after 24 weeks of gestation was greater than the critical blood glucose level [16]. In addition to GDM, the participants were routinely examined to exclude diseases such as multiple pregnancy, and the participants' age, body mass index (BMI), pregnancy period, blood glucose and other clinical data were recorded and counted. All participants were aware of this study and signed informed consent. Meanwhile, blood samples of participants in the fasting state, 1h and 2 h after glucose ingestion were collected, and serum samples were obtained after centrifugation and stored for subsequent assays.

Real-time quantitative PCR assay

TRIzol reagent (Invitrogen, USA) was obtained to extract total RNA from the serum of participants in the fasting state, and cDNA was obtained using the SuperScript II reverse transcriptase kit (Invitrogen, USA). With the help of SYBR® Green PCR kit (TaKaRa, Japan), the reaction system was configured with primers and cDNA as templates, and the detection was performed in 7500 RT PCR system (Applied Biosystems, USA). Glyceraldehyde phosphate dehydrogenase (GAPDH) was used as an internal reference, and the expression of HCG18 was calculated by the $2^{-\Delta\Delta Ct}$ method.

Blood glucose and biochemical index detection

Fasting blood glucose (FBG), 1 h or 2 h blood glucose were measured by glucose oxidase method and continuous glucose monitoring concentration system (CGMS). Triacylglycerol (TG), total cholesterol (TC), and low-density lipoprotein (LDL) were performed using automated standard routine enzymatic methods (Abbott Aeroset, USA).

Statistical analysis

Data analysis was performed by SPSS 17.0 and GraphPad Prism 7.0 software, measurement data were expressed as mean ± standard deviation, and differences between the two groups were tested by Student's t test. Receiver operating characteristic curve (ROC) to evaluate the clinical diagnostic value of HCG18 in GDM. Multivariate logistic analysis was used to verify the relationship between GDM and various indicators. $P < 0.05$ was considered statistically significant.

RESULTS

Clinical data of participants

Table 1 recorded the relevant clinical data of GDM patients and healthy controls. The results showed that there was no significant difference in age, gestational age, fetal birth weight, and LDL among the participants ($p > 0.05$). Besides, there were significant differences in BMI, FBG, 1h blood glucose, 2h blood glucose, TG and TC between the two groups ($p < 0.05$).

LncRNA HCG18 expression was upregulated

Compared with the control group, the relative expression level of HCG18 in the serum of GDM patients was increased via RT-qRCR assays (Fig. 1, $p < 0.001$).

Diagnostic value of HCG18

The diagnostic value of HCG18 in GDM was evaluated by ROC curve. As shown in Figure 2, the area under the curve (AUC) was 0.916, the sensitivity was 80.5%, the specificity was 90.2%, and the 95% confidence interval (CI) was 0.880–0.952, suggesting that HCG18 had a significant performance in the diagnosis of GDM ($p < 0.001$). Multivariate logistic regression analysis verified the relationship between GDM and various indicators, as shown in Table 2 for details. Among all indicators, HCG18 (OR = 6.984, 95% CI = 3.751–13.005, $p < 0.001$) and TG (OR = 1.880, 95% CI = 1.002–3.527, $p = 0.049$) were significantly associated with GDM, which suggested that HCG18 may be a diagnostic factor in GDM patients.

HCG18 expression was positively correlated with blood glucose

The relative expression of HCG18 was positively correlated with fasting blood glucose ($r = 0.6146$, $p < 0.0001$), 1h blood glucose ($r = 0.6979$, $p < 0.0001$) and 2 h blood glucose ($r = 0.7418$, $p < 0.0001$) in GDM patients (Fig. 3A–C).

DISCUSSION

The complex changes in glucose metabolism during pregnancy, including increased glucose requirements, increased insulin resistance, and relative insulin insufficiency, contribute to GDM in some pregnant women [17]. After discussion, it is known that the pregnant women's age, excessive obesity, family genetic history, adverse pregnancy and birth history, hypertension and other factors will be the inducing factors of GDM, resulting in glucose metabolism disorder in pregnant women, affecting normal pregnancy and fetal health [18, 19]. With the application of molecular biology in diseases, it is not uncommon for lncRNAs to be involved in the regulation as diagnostic and prognostic factors. Li et al. [20] explored that RPL13P5 forms a co-expression chain with TSC2 gene through the PI3K-Akt signaling pathway to promote insulin resistance in GDM patients. Another report showed OIP5-AS1 as a potential biomarker of GDM and a regulator of trophoblasts [21]. As mentioned above, HCG18 can play a key regulatory role in a variety of tumors, while its predictive and diagnostic role in GDM has not been clearly reported. However, it has been reported that HCG18 is involved in the regulation of insulin, which is a key factor causing GDM [22].

Collecting the serum of participants for HCG18 expression detection in this study, we found that HCG18 was significantly elevated in GDM patients compared with normal group. Similarly, Ren et al. [23] found that HCG18 is highly expressed in a model of diabetic peripheral neuropathy. In previous GDM studies, MEG8 was also up-regulated and predicted kidney damage [24], SOX2OT was highly expressed in GDM and affected adverse events such as preterm birth and intrauterine death [25], which suggested that the overexpression of HCG18 in GDM has reference value. Fetal macrosomia is one of the most common complications of GDM. Shi and his colleagues [26] confirmed that abnormally expressed lncRNAs may play a partial or key role in the development of GDM macrosomia, providing a potential biological target for the treatment of macrosomia. Besides, excessive obesity can also aggravate the production of GDM, and high expression of lncRNA has been confirmed to be associated with BMI and obesity [27, 28]. We evaluated the significant role of HCG18 in the diagnosis of GDM by ROC curve, and the multivariate logistic regression analysis also verified the close correlation between HCG18 and GDM, suggesting that HCG18 has the diagnostic value of GDM.

Glucose level was used to reflect glucose metabolism level in GDM patients, among which fasting blood glucose, 1-hour blood glucose level and 2-hour blood glucose level are all important diagnostic criteria [29, 30]. By analyzing the relationship between the relative expression of HCG18 and blood glucose in GDM patients, we learned that HCG18 was positively correlated with fasting blood glucose, 1h blood sugar, and 2h blood glucose. It has been reported that miR-195-5p is positively correlated with fasting blood glucose, 1-hour blood glucose and 2-hour blood glucose in GDM patients, which is consistent with the trend of our study [31]. Based on this, it was confirmed that high expression of HCG18 could reflect blood glucose level, and the expression of HCG18 was correlated with the occurrence and development of GDM.

Some GDM patients will return to normal blood sugar levels after pregnancy under reasonable management and treatment, but there are still patients who will develop type 2 diabetes or other complications, and the probability is increasing. This study used the expression level of HCG18 to effectively predict and diagnose GDM, which can provide a certain theoretical basis for the clinical treatment of GDM. However, if it is to be truly applied to the clinic, it is necessary to increase the number of samples for experimentation and verification, and we will also pay attention and implement it in the follow-up research.

CONCLUSIONS

In general, this study stated that the expression of lncRNA HCG18 is upregulated in GDM serum and confirmed that HCG18 has the potential to diagnose GDM, speculating that HCG18 may become a biomarker for GDM.

Article information and declarations

Data availability statement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics statement

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Central Hospital of Enshi Tujia and Miao Autonomous Prefecture. All participants were aware of this study and signed informed consent.

Author contributions

All authors designed this study. LC and JJ conducted the experiment, analyzed the data and wrote the manuscript. YT revised the manuscript. All authors reviewed and approved for publication.

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None.

Conflict of interest

There is no conflict of interest in this study.

Supplementary material

None.

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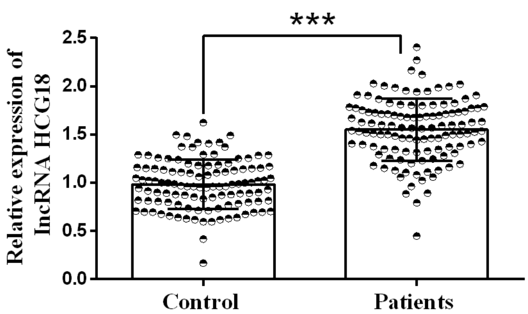

Figure 1. The relative expression level of HCG18 in serum of gestational diabetes mellitus (GDM) patients was increased compared with healthy controls; *p < 0.001, compared with the controls

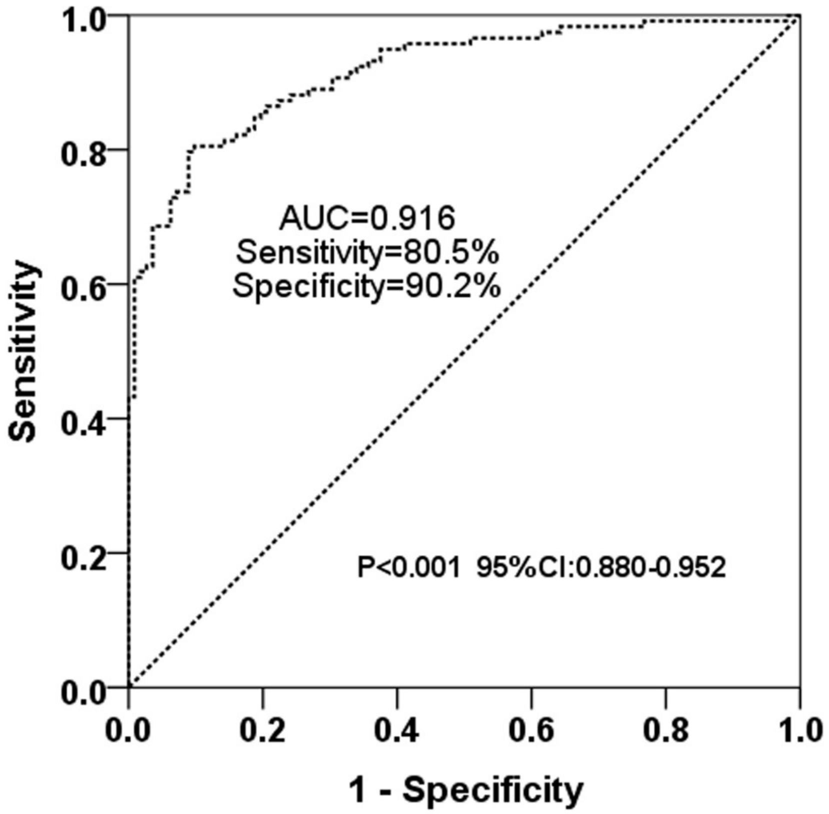

Figure 2. Receiver operating characteristic curve (ROC) curve of HCG18; AUC — area under the curve; CI — confidence interval

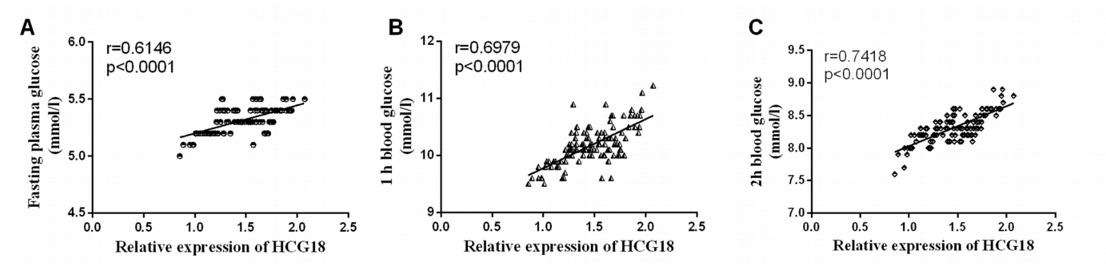

Figure 3. HCG18 expression was positively correlated with blood glucose; **A.** The expression of HCG18 was positively correlated with fasting blood glucose ($r = 0.6146$, $p < 0.0001$); **B.** The expression of HCG18 was positively correlated with 1h blood sugar ($r = 0.6979$, $p < 0.0001$); **C.** The expression of HCG18 was positively correlated with 2 h blood sugar ($r = 0.7418$, $p < 0.0001$)

Table 1. Comparison of clinical data between gestational diabetes and healthy individuals

Paraments	Total (n = 230)		p value
	Control (n = 112)	Patients (n = 118)	
Age [years]	29.57 ± 0.97	29.48 ± 0.93	0.439
BMI [kg/m^2]	24.65 ± 2.78	25.94 ± 3.12	0.001
Gestational age [weeks]	26.89 ± 1.03	27.05 ± 1.46	0.334
FBG [mmol/L]	4.45 ± 0.31	5.30 ± 0.11	< 0.001
1 h blood glucose [mmol/L]	6.32 ± 0.20	10.20 ± 0.30	< 0.001
2 h blood glucose [mmol/L]	5.51 ± 0.40	8.29 ± 0.20	< 0.001
Fetal birth weight [g]	3426.38 ± 276.75	3448.92 ± 178.91	0.462
TG [mg/dL]	1.00 ± 0.28	1.34 ± 0.33	< 0.001
TC [mg/dL]	5.45 ± 0.34	5.89 ± 0.45	< 0.001
LDL [mg/dL]	2.63 ± 0.36	2.72 ± 0.51	0.110

BMI — body mass index; FBG — fasting blood glucose; TG — triglycerides; TC — total cholesterol; LDL — low density lipoprotein; Data are expressed as n or mean ± standard deviation (SD)

Table 2. Relationship between gestational diabetes mellitus and various indicators

Indicators	Multivariate logistic analysis		
	OR	95% CI	p value
LncRNA HCG18	6.984	3.751–13.005	< 0.001
Age [years]	1.410	0.758–2.621	0.277
BMI [kg/m^2]	1.733	0.922–3.257	0.088
Gestational age [weeks]	1.173	0.623–2.211	0.621
Fetal birth weight [g]	1.308	0.702–2.437	0.398
TG [mg/dL]	1.880	1.002–3.527	0.049
TC [mg/dL]	1.416	0.766–2.620	0.267
LDL [mg/dL]	1.216	0.659–2.243	0.531

CI — confidence interval; BMI — body mass index; TG — triglycerides; TC — total cholesterol; LDL — low density lipoprotein