RESEARCH ARTICLE

Maternal IGF1 and IGF1R polymorphisms and the risk of spontaneous preterm birth

Jian-Rong He^{1†} | Yu-Mian Lai^{2†} | Hui-Hui Liu^{1†} | Guang-Jian Liu¹ | Wei-Dong Li¹ |
Xue-Jiao Fan¹ | Xue-Ling Wei¹ | Xiao-Yan Xia¹ | Ya-Shu Kuang¹ | Xiao-Dan Liu¹ |
Nian-Nian Chen¹ | Jin-Hua Lu¹ | Qiao-Zhu Chen² | Wei-Bi Mai² | Hui-Min Xia¹ |
Xiu Qiu¹

¹Division of Birth Cohort Study, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, Guangzhou, China

²Department of Obstetrics and Gynecology, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, Guangzhou, China

Correspondence

Xiu Qiu and Hui-Min Xia, Division of Birth Cohort Study, Guangzhou Women and Children's Medical Center, Guangzhou, China. Emails: qxiao0161@163.com (XQ) and huimin.xia876001@gmail.com (H-MX)

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Background: The insulin-like growth factor (IGF) pathway was involved in the occurrence of spontaneous preterm birth (SPTB), but little is known regarding the relationship between genetic variations in IGF pathway and the risk of SPTB. We aimed to investigate the associations of *IGF1* rs972936 and *IGF1* receptor (*IGF1R*) rs2229765 polymorphisms with SPTB risk in a Chinese population.

Method: A total of 114 cases of SPTB and 250 controls of term delivery were included from Guangzhou Women and Children's Medical Center, China. The odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) were calculated using multivariate logistic regression.

Results: We found that the GA and GA/AA genotypes of *IGF1* rs972936 were associated with an increased risk of SPTB, and the adjusted ORs (95% CI) were 1.74 (1.01-3.02) and 1.75 (1.04-2.93) respectively. Women carrying GA and GA/AA genotypes of *IGF1R* rs2229765 had a reduced risk compared to those with the GG genotype (0.60 [0.37-0.98] and 0.64 [0.40-1.00] respectively). There were significant interactions between *IGF1* rs972936 and GDM status (P for interaction=.02), as well as between *IGF1R* rs2229765 and pre-pregnancy BMI (P for interaction <.001) on the risk of SPTB.

Conclusion: Our findings suggest that polymorphisms of *IGF1* rs972936 and *IGF1R* rs2229765 were associated with the risk of SPTB in Chinese pregnant women and these effects depend on the maternal metabolic status.

KEYWORDS

IGF1, *IGF1R*, polymorphism, spontaneous preterm birth, susceptibility

1 | INTRODUCTION

Preterm birth (PTB), defined as birth before 37 weeks of gestation, is the leading cause of neonatal death and contributes to short- and long-term morbidity of various diseases, including cerebral palsy, developmental delay, retinopathy of prematurity, and hearing and vision problems.¹ PTB affects 5%-18% of pregnancies depending on geographical areas and has become a major public health problem. Around

70% of PTB are spontaneous (SPTB), caused by spontaneous preterm labour or preterm premature rupture of the membranes (PPROM).² The aetiology of SPTB remains unclear.^{3, 4} Genetic predisposition has been shown to play an important role in the aetiology of SPTB.⁵ Previous studies focused on the single nucleotide polymorphisms (SNPs) in genes related to maternal immune response (particularly the inflammatory pathways).⁶

The insulin-like growth factor (IGF) 1 is a key modulator of cell proliferation, differentiation, and apoptosis.⁷ Animal studies have shown that

[†]These authors contributed equally to this work.

IGF1 promotes placental differentiation and function in early pregnancy, and that circulating IGFs are important regulators of placental growth and functional development.⁸ A recent study showed that the expression of *IGF1* decreased in the placenta of preterm birth compared to those of full term birth.⁹ It was also reported that preterm neonates have lower cord blood levels of IGFs than those for term neonates.¹⁰ Together, these data strongly suggest that alterations in the *IGF1* levels play a role in the occurrence of SPTB. Thus, SNPs related to *IGF1* levels may affect the risk of SPTB. However, there is little evidence regarding the relationship between genetic variations in *IGF* system and the risk of SPTB.

Recent studies found two SNPs, *IGF1* rs972936 (G>A) and *IGF1* receptor (*IGF1R*) rs2229765 (G>A), were related to the circulating *IGF1* levels.^{11–13} In the present study, for the first time we investigated whether the maternal *IGF1* rs972936 and *IGF1R* rs2229765 were associated with the risk of SPTB in a Chinese population. Because IGFs are nutrition-related peptides,¹⁴ it is possible that the functional output of this pathway depends on nutritional or metabolic status. Indeed, in the context of cancer, there is a significant interaction between polymorphisms in *IGF1* and *IGF1R* genes and metabolic risk factors (eg, diabetes, body mass index [BMI]).^{15–17} Therefore, we further assessed whether the associations of these two SNPs with SPTB risk were modified by maternal metabolic factors. To the best of our knowledge, there have been no studies exploring the interaction between IGF system and metabolic risk factors on the risk of SPTB.

2 | MATERIALS AND METHODS

2.1 | Subjects

This case-control study was part of a prospective study in Guangzhou Women and Children's Medical Center (GWCMC) that was designed to explore the effects of genetic and environmental factors on pregnancy outcomes and the health of the offspring. During the routine oral glucose tolerance test at 24–28 weeks of gestation, pregnant women were invited to participate in the study if they met the following inclusion criteria: ≥ 18 years old Chinese and with the intent to deliver at GWCMC. A total number of 3597 (response rate, 69.0%) pregnant women were recruited to this study between April 2013 and March 2014. Blood samples were collected at the time of enrolment and stored at -80°C until used. Among the pregnant women who gave singleton live birth, 174 women had preterm deliveries (length of gestation <37 weeks).

After excluding women with medically indicated preterm delivery ($n=53$), in vitro fertilization ($n=5$), fetal anomaly ($n=1$) or uterine malformation ($n=1$), a total of 114 spontaneous preterm deliveries (42 preterm labour and 72 PPROM) were included in the present study in the case group. Controls were selected from pregnant women who delivered singleton term babies (gestational age of 38–41 weeks), without preeclampsia, eclampsia, placental abruption, placenta praevia, and haemolysis, elevated liver enzymes and low platelet count syndrome. Controls were frequency-matched to the cases for age groups. A total of 250 controls were included. Informed consent was obtained

from all participants, and this study was approved by the institutional review board of GWCMC.

2.2 | Genotyping

Genomic DNA was extracted from cells isolated from 2 mL of peripheral blood of each participant using the QIAGEN DNA Blood Mini Kit (Qiagen, Valencia, CA, USA) according to the manufacturer's instructions. Genotyping was performed using a MassARRAY system (Sequenom) in Beijing CapitalBio Corporation, Beijing, China. The details of the primers are described in Table S1. To evaluate the quality of genotyping, 20 samples (5.5% of total) were tested in duplicates; concordance rates were 100%. DNA from 2 (0.5%) samples failed to be genotyped for *IGF1* rs972936 and *IGF1R* rs2229765.

2.3 | Clinical data

The following information was obtained using a face to face questionnaire at the recruitment: mother's age, educational level, marital status, pre-pregnancy weight, height and parity. Additional data, including gestational diabetes mellitus (GDM) status, gestational age at delivery, infant's gender and birth weight, were abstracted from medical records after delivery. Gestational age was confirmed by clinicians based on the ultrasound examination in the first or second trimester.

2.4 | Statistical analysis

The differences in demographic and clinical characteristics between the cases and controls were assessed using the χ^2 test or Fisher's exact test for categorical variables and Student's *t* test for continuous variables. The Hardy-Weinberg equilibrium for *IGF1* rs972936 and *IGF1R* rs2229765 was tested by a goodness-of-fit χ^2 test to compare the observed genotype frequencies with the expected frequencies in the control group. No deviation from the Hardy-Weinberg equilibrium was observed ($P=.94$ and $.41$ for rs972936 and rs2229765 respectively).

Associations between genotypes and the risk of SPTB were evaluated using multivariate logistic regression, and the odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were calculated. The logistic models were firstly adjusted (model 1) for parity (primiparous vs multiparous), and infant's gender (female vs male), and then further adjusted (model 2) for maternal age, educational level (high school or below vs college or above) and metabolic factors (pre-pregnancy BMI and GDM status). We also calculated a genetic risk score for each individual as a sum of the number of risk alleles for the *IGF1* rs972936 (A allele) and the *IGF1R* rs2229765 (G allele). The genetic risk score was included in the logistic regression as a continuous variable. The differences in mRNA levels for different genotypes were compared were evaluated by *t* test.

We further performed stratified analysis to examine whether the associations of genotypes with the risk of SPTB were modified by pre-pregnancy BMI (<20 vs ≥ 20 kg/m²) and GDM status (no vs yes). In our population, the proportion of overweight women (BMI ≥ 24 kg/m²)

was low (4.4%). Considering the sample size, we chose the 20 kg/m² of BMI (the mean value in our study) as the cut-off value to perform stratified analysis. The multiplicative interaction between genotypes and pre-pregnancy BMI (binary or continuous variables) and GDM status were evaluated by including the product terms in multivariate regression models.

Statistical significance was set at a two-tailed *P*-value of <.05. All statistical analyses were performed using SAS statistical software version 9.3 (SAS Institute Inc., Cary, NC, USA).

3 | RESULTS

Baseline characteristics for these participants are shown in Table 1. There were no statistically significant differences in maternal age, educational level, marital status, pre-pregnancy BMI, or GDM status between cases and controls. However, cases were more likely to be multiparous (*P*=.01), and there was a higher percentage of boys (*P*=.001) and lower birth weight (*P*<.001) among neonates from the case group compared to the control group.

Table 2 presents the allele frequencies and allelic association of the *IGF1* rs972936 and *IGF1R* rs2229765 with SPTB. Compared to the control group, women of case group tended to have a higher percentage of *IGF1* rs972936 A allele and a lower percentage of *IGF1R* rs2229765 A allele, but the difference is not statistically significant (Table 2). Table 3 shows the associations between genotypes and the risk of SPTB. In model 1 (adjusted for maternal parity and infant gender), the GA or GA/AA genotypes were associated with an increased risk of SPTB (adjusted OR, 1.67 [0.97-2.87] and 1.69 [1.01-2.83], respectively) compared to the homozygous genotype GG. For the *IGF1R* rs2229765 polymorphism, we found that women carrying the GA or GA/AA genotypes had a reduced risk of delivering SPTB compared to those with the GG genotype (0.60 [0.37-0.99] and 0.63 [0.40-0.99] respectively). After further adjusted for other covariates (model 2), the effect size of SNPs remained similar. As for the genetic risk score, multivariate logistic regression showed 1-unit increase in score was associated with a 33% increased risk of SPTB (95% CI, 4%-69%; Table 3).

We further performed stratified analysis to evaluate whether the associations between genetic variants and the risk of SPTB were modified by maternal metabolic factors (Table 4). The increased risk of delivering SPTB was more pronounced among women with *IGF1* rs972936 GA/AA genotype and without GDM (adjusted OR, 2.33 [1.27-4.29])

TABLE 1 Characteristics of participants

Characteristics	Cases, n (%)	Controls, n (%)	<i>P</i> value
<i>Mothers</i>			
<i>Age (y)</i>			
<30	55 (48.3)	127 (50.8)	.65
≥30	59 (51.8)	123 (49.2)	
Mean (SD)	29.8 (3.5)	29.8 (3.5)	.97
Range	20-41	22-41	
<i>Educational level</i>			
High/middle school or below	12 (10.5)	36 (14.4)	.31
College or above	102 (89.5)	214 (85.6)	
<i>Marital Status</i>			
Unmarried	0 (0.0)	2 (0.8)	1.00 ^a
Married	114 (100.0)	248 (99.2)	
<i>Parity</i>			
Primiparous	92 (80.7)	225 (90.0)	.01
Multiparous	22 (19.3)	25 (10.0)	
<i>Pre-pregnancy BMI</i>			
<20	74 (64.9)	169 (67.6)	.61
≥20	40 (35.1)	81 (32.4)	
Mean (SD)	20.0 (2.1)	19.8 (2.1)	.53
<i>GDM</i>			
No	88 (77.2)	201 (80.4)	.48
Yes	26 (22.8)	49 (19.6)	
<i>Newborns</i>			
<i>Gender</i>			
Female	46 (40.4)	145 (58.0)	.002
Male	68 (59.7)	105 (42.0)	
Birth weight (g), median (25th, 75th)	2660 (2300, 2880)	3280 (3030,3540)	<.001
Gestational age (wk),median (25th, 75th)	36 (35,36)	39 (39, 40)	<.001

^aFisher's exact test.

compared to that of women with GDM (*P* for interaction=.02). In addition, the protective effects of *IGF1R* rs2229765 GA/AA genotypes were more evident among women with high pre-pregnancy BMI

TABLE 2 Allelic association of the *IGF1* rs972936 and *IGF1R* rs2229765 variants with PTB

Genotype	Cases n (%)	Controls n (%)	Odds ratio (95% CI) ^a	<i>P</i>
<i>IGF1</i> rs972936				
G	117 (51.3)	287 (57.9)	1.00 (ref)	
A	111 (48.7)	209 (42.1)	1.30 (0.95,1.79)	.099
<i>IGF1R</i> rs2229765				
G	159 (69.7)	316 (63.7)	1.00 (ref)	
A	69 (30.3)	180 (36.3)	0.76 (0.54,1.07)	.112

^aCrude odds ratio.

TABLE 3 Associations of genetic variants with the risk of preterm birth

Genotype	Cases n (%)	Controls n (%)	Model 1 ^a		Model 2 ^b	
			Odds ratio (95% CI)	P	Odds ratio (95% CI)	P
IGF1 rs972936						
GG	29 (25.4)	85 (34.3)	1.00 (ref)		1.00 (ref)	
GA	59 (51.8)	117 (47.2)	1.67 (0.97,2.87)	.066	1.74 (1.00-3.01)	.048
AA	26 (22.8)	46 (18.6)	1.74 (0.90,3.36)	.099	1.72 (0.88-3.35)	.111
GA/AA	85 (74.6)	163 (65.7)	1.69 (1.01,2.82)	.045	1.73 (1.03-2.91)	.037
IGF1R rs2229765						
GG	57 (50.0)	94 (37.9)	1.00 (ref)		1.00 (ref)	
GA	45 (39.5)	128 (51.6)	0.60 (0.37,0.97)	.037	0.60 (0.37-0.98)	.042
AA	12 (10.5)	26 (10.5)	0.77 (0.35,1.68)	.510	0.79 (0.36-1.73)	.553
GA/AA	57 (50.0)	154 (62.1)	0.63 (0.40,0.99)	.045	0.64 (0.40-1.01)	.054
Genetic risk score Continuous (mean, SD) ^c	2.4 (1.0)	2.1 (1.0)	1.33 (1.05-1.69)	.021	1.33 (1.04-1.69)	.023

^aAdjusted for parity and infant gender.^bAdjusted for maternal age, educational level, parity, infant gender, pre-pregnancy BMI, and status of GDM.^cThe genetic risk score was calculated by adding up the number of risk alleles for the *IGF1* rs972936 (A allele) and the *IGF1R* rs2229765 (G allele).**TABLE 4** Stratified analysis for associations between genetic variants and the risks of preterm birth

	IGF1 rs972936			IGF1R rs2229765		
Stratified variables	Genotype	Case/control	OR (95% CI) ^a	Genotype	Case/control	OR (95% CI) ^a
Pre-pregnancy BMI						
<20	GG	19/57	1.00 (ref)	GG	28/67	1.00 (ref)
	GA/AA	55/110	1.79 (0.93, 3.43)	GA/AA	46/100	1.22 (0.68, 2.21)
≥20	GG	42671.00	1.00 (ref)	GG	29/27	1.00 (ref)
	GA/AA	30/53	1.84 (0.76, 4.44)	GA/AA	11/54	0.14 (0.05, 0.34)
	P for interaction		.9			<.001
GDM						
No	GG	20/72	1.00 (ref)	GG	47/73	1.00 (ref)
	GA/AA	68/127	2.33 (1.27, 4.29)	GA/AA	41/126	0.52 (0.31, 0.88)
Yes	GG	9/13	1.00 (ref)	GG	10/21	1.00 (ref)
	GA/AA	17/36	0.59 (0.19, 1.86)	GA/AA	16/28	1.26 (0.43, 3.74)
	P for interaction		.02			.15

^aAdjusted for maternal age, educational level, parity, pre-pregnancy BMI, status of GDM, and infant gender.

(adjusted OR, 0.14 [0.05-0.34]) compared to that of women with low pre-pregnancy BMI (P for interaction $P<.001$). We also included the pre-pregnancy BMI as a continuous variable in the interaction analysis, and the interaction term remained significant ($P<.01$).

4 | DISCUSSION

In the present study, we firstly reported *IGF1* rs972936 and *IGF1R* rs2229765 were associated with the risk of SPTB in a Chinese population. Specifically, women with GA or GA/AA genotypes of *IGF1R* rs2229765 had a reduced risk of delivering SPTB compared to those

with the GG genotype, while women carrying the GA or GA/AA genotypes of *IGF1* rs972936 had an increased risk compared to those with the GG genotype. Moreover, the stratified analysis showed that the protective effect of *IGF1R* rs2229765 GA/AA genotypes were more evident among women with high pre-pregnancy BMI, while the predisposing effect of *IGF1* rs972936 GA/AA genotypes was more pronounced among women without GDM.

Few studies have explored the relationship between genetic variations in the IGF system and the risk of SPTB. A previous study conducted in Chile found that *IGF1* rs5742612 was associated with SPTB risk,¹⁸ while this SNP was reported to have no correlation with the levels of circulating IGF1.¹⁹⁻²¹ In the present study, women with GA

or GA/AA genotypes of *IGF1* rs972936, which is located in intron region, had an increased risk of SPTB compared to those with the GG genotype. A previous study of European Alzheimer's disease patients showed that individuals with AG and AA genotypes of *IGF1* rs972936 had lower serum IGF1 levels compared to those with the GG genotype.¹¹ Furthermore, another *IGF1* SNP, rs1520220, is in strong linkage disequilibrium with rs972936 and is also associated with circulating IGF1 levels in European women.²² Former literature reported that cord serum levels of total and free IGF1 was significantly lower in preterm than in term neonates.¹⁰ Thus, we speculate that the A allele of rs972936 could infer greater risk for SPTB through its effect of lowering the IGF-I level.

The *IGF1R* gene was originally linked to has also been associated with preterm PTB through a linkage analysis in a Finnish population, which observed two fetal SNPs in *IGF1R* (rs7165181 and rs4966038), but not maternal SNPs were associated with SPTB risk.²³ In the present study, we found that the maternal GA/AA genotype of *IGF1R* rs2229765 was significantly associated with a reduced risk of SPTB compared to the GG genotype. The A/G polymorphism of rs2229765, located in exon area, is a synonymous polymorphism leading to the amino acid change Glu->Glu at position 1043 and has been shown to regulate alternative splicing of *IGF1R* mRNA.²⁴ The A allele of *IGF1R* rs2229765 has been linked to lower levels of free plasma IGF1, and is reportedly more frequent among long-lived people.¹³ Nevertheless, another study showed that the AA/AG genotype of *IGF1R* rs2229765 was associated with higher plasma IGF1 levels and a higher risk of developed advanced colorectal cancer.¹² Therefore, further studies are needed to determine the functional or structural effects of *IGF1R* rs2229765 polymorphism on the IGF signaling system.

In the stratified analysis, we found that the effects of *IGF1* rs972936 and *IGF1R* rs2229765 on the risk of SPTB varied depending on maternal metabolic status (pre-pregnancy BMI or GDM status). Although the mechanisms underlying these interactions remain unclear at present, there are several plausible explanations. *IGF1R* and insulin receptors are structurally homologous, and insulin could also bind to *IGF1R* and activate IGF signalling.²⁵ We speculate that GA or GA/AA genotypes of *IGF1* rs972936 increase preterm risk as they lead to downregulation of *IGF1* expression, while the hyperinsulinaemia induced by GDM could activate IGF signaling by binding of insulin to *IGF1R*. Thus, there may be an antagonistic effect between *IGF1* rs972936 and GDM status regarding the risk of preterm birth. On the other hand, a previous study has shown that adult IGF1 level was positively related to BMI when BMI was below the level of obesity.²⁶ Recent studies also revealed that maternal circulating IGF1 level during pregnancy was significantly correlated with maternal BMI.^{28,29} We found the GA/AA genotype of *IGF1R* rs2229765 was significantly associated with a reduced risk of SPTB. High BMI, which might induce high IGF1 level, combined with the GA/AA genotype of *IGF1R* rs2229765 might engender more active IGF signaling, and thereby have a synergistic effect on the risk of SPTB.

The present study has some limitations. First, we analysed a limited set of SNPs from *IGF1* and *IGF1R* genes. Second, this was a

hospital-based study, which might not be representative of the general population. Third, because of the relatively small sample size, the statistical power of the present study for *IGF1* rs972936 and *IGF1R* rs2229765 were 57% and 50%, respectively. We also calculated the false-positive report probability,⁹ and results showed that only the genetic risk score remained significant at the prior probability level of 0.1. In addition, we were also unable to categorize the preterm cases into late (34-36 weeks of gestation), moderate (32-33 weeks) and very (<32 weeks) preterm birth. Admittedly, further studies with a larger and independent cohort are needed to replicate the current findings. Fourth, we did not have data regarding fetal genotype, which also contributes to SPTB risk.^{30,31}

In conclusion, we firstly observed polymorphisms of *IGF1* rs972936 and *IGF1R* rs2229765 were associated with the risk of SPTB in a Chinese population. We also found that these associations varied according to maternal metabolic status (pre-pregnancy BMI or GDM status). These findings might have important implications for prediction and intervention for SPTB. However, further studies with larger sample sizes will be required to confirm the relationship between the IGF system and SPTB.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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