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Association between *FcγRIIB* Gene Polymorphism, Periodontitis and Pregnancy-induced Hypertension in Chinese Pregnancy Women

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Abstract: *Objective:* Research suggests a link between maternal periodontitis and pregnancy-induced hypertension (PIH). As an immunoglobulin G (IgG) receptor, *FcγRIIB* delivers inhibitory signals to B lymphocytes. Previous studies have demonstrated that *FcγRIIB*-232I/T polymorphism is associated with periodontitis, and the link between 232T allele carriers and periodontitis may stem from their reduced IgG antibody responses to *P. gingivalis*. The role of *FcγRIIB*-232I/T polymorphism in predisposing Chinese pregnant women to periodontitis and PIH was explored in this investigation. *Methods:* Clinical periodontal parameters and obstetric records were retrospectively analyzed in 87 Chinese pregnant women. *FcγRIIB*-232I/T genotyping was performed using genomic DNA isolated from peripheral blood samples from each participant. The expression levels of *FcγRIIb* on peripheral B lymphocytes from 10 women were measured by flow cytometry. *Results:* The *FcγRIIB*-232T allele was associated with elevated third-trimester blood pressure, with compounded effects observed in carriers concurrently affected by periodontitis. Periodontitis and PIH exhibited a shared genetic predisposition through the *FcγRIIB*-232I/T polymorphic locus. Among individuals carrying the *FcγRIIB*-232T allele, periodontitis was significantly associated with PIH. *Conclusion: FcγRIIB*-232T allele carriers of Chinese pregnancy women are more susceptible to periodontitis and PIH,and those with periodontitis are more susceptible to PIH.

Keywords: *FcγRIIB* gene polymorphism; Periodontitis; Pregnancy-induced hypertension

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1. Introduction

The ITIM-containing cytoplasmic architecture of *FcγRIIb* establishes its unique position as the sole inhibitory

member of the Fc receptor family [1]. Functional studies reveal that IgG complex-mediated co-ligation of *FcγRIIb* and BCR triggers ITIM-dependent tyrosine phosphorylation events that negatively regulate BCR signaling amplitude [2,3]. Pathophysiological observations in *FcγRIIb*-knockout mice, characterized by severe immune complex-induced inflammatory syndromes, validate its critical role in maintaining immunological equilibrium [4,5].

Systemic maternal infections may increase risks of placental infection, preterm birth and premature rupture of membranes through inflammatory cytokines and prostaglandin release [6,7]. Periodontitis, a chronic inflammatory oral condition, is involved in the pathogenesis of gestational hypertensive disorders, particularly PIH and preeclampsia [8–11].

11 single-nucleotide polymorphisms (SNPs) have been confirmed to be FcγRIIB-specific of which to be associated with periodontitis. Yasuda et al. [12] demonstrated distinct associations between FcγRIIB genetic variations and periodontitis subtypes through case-control analysis. Their investigation revealed a statistically significant variation in the allelic distribution of the FcγRIIB gene polymorphism at exon5 (nt232I/T) when comparing subjects with aggressive periodontitis to healthy individuals, where the 232T allele exhibited higher prevalence in the disease cohort. Additionally, the study identified differential patterns in the intronic region (nt646-184A/G) of this gene, with the 646-184A variant showing increased frequency in chronic periodontitis patients relative to non-diseased controls. These findings suggest subtype-specific genetic predispositions involving distinct regulatory domains of the FcγRIIB receptor in periodontal pathogenesis. Prior investigations have identified associations between the FcγRIIB-nt645+25A/G polymorphism and multiple gestational complications, including periodontal disease, preterm delivery accompanied by low birth weight, as well as PIH and preeclampsia in maternal populations [11,13]. However, the mechanism of these associations remains unclear.

Emerging evidence suggests a potential mechanistic link between periodontal pathogenesis and pregnancy complications. Subgingival microbial colonization induces systemic inflammation through elevated circulating proinflammatory mediators, which may propagate to the chorioamniotic membranes, potentially contributing to gestational disorders. Particularly, imbalanced Th1/Th2 cytokine profiles characterized by elevated interleukin-1β and IL-6 concentrations have been significantly associated with preterm deliveries occurring before 35 weeks' gestation and histologically confirmed chorioamnionitis [14]. Of clinical relevance, genetic variations in *FcγRIIB* (specifically nt232I/T and nt645+25A/G loci) have been implicated in periodontal disease pathogenesis. Functional analyses reveal that the 232T/nt645+25AA haplotype correlates with attenuated IgG-mediated responses to *Porphyromonas gingivalis* antigens [15,16], concomitant with enhanced *FcγRIIb* receptor expression on B-lymphocytes in AA genotype carriers relative to GG individuals [15]. This immunogenetic profile suggests a biological plausibility for *FcγRIIb* polymorphisms modulating host-inflammatory responses to periodontal pathogens, potentially establishing a proinflammatory milieu that could adversely affect pregnancy maintenance through cytokine-mediated pathways.

This study aims to investigate whether the *FcgRIIB*-nt232I/T polymorphism is associated with periodontitis and/or PIH in Chinese pregnant women, and to further explore the potential mechanisms involved.

2. Materials and methods

2.1. Subjects

This study enrolled 200 pregnant women (mean age: 37.89 years old) who were referred to the Department of Obstetrics and Gynecology, HMU4 (Fourth Affiliated Hospital, Harbin Medical University), and delivered live

infants (Oct 2015–Oct 2019). This study implemented rigorous exclusion criteria to minimize confounding: (1) Pre-existing medical conditions (hypertension, hepatitis B, anemia, diabetes, psychiatric disorders, renal/genetic diseases); (2) Obstetric risks (multifetal gestation, cervical insufficiency, placental anomalies) [13]; (3) Substance exposure (active smoking post-conception, alcohol/drug abuse); (4) Nutritional compromise. The inclusion criteria were selected based on documented confounding variables and established risk predictors for obstetric complications, as delineated in prior epidemiological studies [11]. Following rigorous screening protocols, the analytical cohort ultimately included 87 eligible participants. All enrolled subjects provided written informed consent through standardized documentation prior to parturition. This consent procedure underwent ethical review and received formal certification from the Institutional Review Board of Harbin Medical University, ensuring compliance with the Declaration of Helsinki guidelines.

2.2. Clinical assessment

Perinatal records were retrospectively abstracted from the obstetrical database of HMU4. PIH diagnosis adhered to China's gestational hypertension management guidelines (CSOG-2020), requiring sustained blood pressure elevation (SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg) on two consecutive readings post-20 gestational weeks. Embryonic age determination utilized the Naegele formula, with gestational dating anchored to the initial day of the last confirmed menstrual cycle.

2.3. Periodontal examination

Periodontal evaluations were systematically conducted during gestational weeks 16–24 by three trained clinicians blinded to maternal health status. Standardized oral assessments included multilevel diagnostic parameters: (1) Probing depth measurements quantifying connective tissue detachment (recorded at six anatomical locations per dental unit), reflecting cumulative periodontal destruction; (2) Gingival bleeding index documentation as an inflammatory activity indicator; (3) Microbial accumulation quantification through visible plaque index scoring. Case definition followed established epidemiological criteria, requiring ≥ 60% of examined sites to demonstrate ≥ 3 mm clinical attachment loss, a threshold indicative of significant periodontal breakdown [17].

2.4. FcγRIIB-nt232I/T genotyping protocol

Genetic material extraction from venous blood samples was conducted using commercial isolation reagents (Easy-DNA system, Invitrogen, San Diego, CA). Purified nucleic acid aliquots were cryopreserved at 4 ℃ pending molecular analysis. Target gene amplification employed a nested PCR strategy adapted from established protocols12. Initial amplification targeted the *FcgRIIB* locus using intronic primers (spanning introns 3–6), designed to circumvent sequence homology between *FcgRIIB* and the homologous *FcgRIIC* locus. Amplimers underwent restriction enzyme digestion and purification before serving as templates for secondary amplification focusing on exon5 sequences. The exon-specific reaction utilized a 25 μL amplification system containing 1.25 U ExTaq polymerase, with 30 ng template DNA subjected to initial denaturation (95 ℃ × 5 min), followed by 35 cycles of three-step amplification (94 ℃ × 30 s, 60 ℃ × 30 s, 72 ℃ × 30 s), concluding with terminal extension (72 ℃ × 5 min).

2.5. FcγRIIB expression levels on peripheral B lymphocytes

The expression levels of *FcγRIIb* on peripheral B lymphocytes were compared among *FcγRIIB*-232I/T genotypes in 10 Chinese pregnancy women volunteers. Present smokers were excluded. Five millilitres of

EDTA-anticoagulated peripheral blood was obtained from each subject. Erythrocytes were lysed by incubation with ammonium chloride. Following three PBS rinsing cycles (300 g × 5 min), cellular suspensions underwent sequential immunolabeling procedures. Primary incubation utilized monoclonal antibody clone 41H.16 (mouse origin) paired with species-matched FITC-conjugated $F(ab')_2$ secondary reagents (1:200 dilution, 30 min RT). Subsequent pre-blocking with homologous serum (10% v/v, 15 min) preceded counterstaining with PE-labeled anti-CD19 lineage markers (clone HIB19, 20 μL/test). Viable cell populations were discriminated through 7-AAD viability dye exclusion (5 μL/test, 10 min incubation). Processed samples were vortex-mixed in staining buffer and subjected to flow cytometric analysis (BD FACSCanto II), with *FcγRIIb* expression quantitation determined by median fluorescence intensity (MFI) of $CD19^+$lymphocyte subsets.

2.6. Statistical analysis

The correlation between pregnancy-induced hypertension (PIH) and periodontitis was analyzed using nonparametric Mann-Whitney U tests. Categorical analyses of *FcγRIIB*-nt232I/T genotypic distributions versus PIH status employed chi-square tests, with Fisher's exact substitution applied when expected cell frequencies fell below 5. For quantitative comparisons of *FcγRIIb* receptor density on B lymphocytes, nonparametric comparative analyses were implemented based on data distribution characteristics. Statistical analyses were conducted using Stat View with significance threshold at $P < 0.05$.

3. Results

Based on determination of *FcγRIIB*-232I/T genotypes, the 87 Chinese pregnancy women were separated into *FcγRIIB*-232T carriers group ($n = 61$) and T non-carriers group ($n = 26$) in **Table 1**. 232-T carriers exhibited: Higher periodontitis prevalence ($P = 0.041$); Elevated third-trimester blood pressure (Systolic blood pressure, SBP, $P = 0.031$; Diastolic blood pressure, DBP, $P = 0.021$). No significant intergroup differences emerged in postpartum blood pressure or clinical periodontal parameters (**Table 1**).

Table 1. Clinical characteristics between *FcγRIIB*-nt232T carriers and non-carriers

	***FcγRIIB*-nt232T carriers ($n = 61$)**	***FcγRIIB*-nt232T non-carriers ($n = 26$)**	***P*-value**
Periodontitis (+)	13 (21%)	1 (4%)	0.0411*
CAL (mm)	2.5 ± 0.5	2.5 ± 0.4	0.3624
Bleeding on probing (%)	12.4 ± 15.8	14.0 ± 16.7	0.7883
Plaque control record (%)	35.7 ± 22.5	30.1 ± 20.8	0.3252
Gestational age at delivery (weeks)	36.68 ± 3.56	40.12 ± 4.73	0.1767
SBP at the third trimester	134.35 ± 8.75	115.67 ± 13.22	0.0314*
DBP at the third trimester	83.34 ± 5.04	72.15 ± 9.75	0.0211*
SBP after delivery	129.08 ± 9.97	120.89 ± 16.12	0.1040
DBP after delivery	80.63 ± 5.75	74.67 ± 9.34	0.1441

Based on periodontal and obstetric records, the *FcgRIIB*-232T carriers of Chinese pregnant women were

separated into periodontitis group (n = 13) and non-periodontitis (n = 48) in **Table 2**. The level of SBP (P = 0.0106) and DBP (P = 0.0193) at the third trimester were significantly higher in the periodontitis of *FcgRIIB*-232T carriers group compared with the non-periodontitis of *FcgRIIB*-232T carriers group, however, the level of SBP and DBP after delivery were not significantly higher in the periodontitis of *FcgRIIB*-232T carriers group compared with the non-periodontitis of *FcgRIIB*-232T carriers group.

Table 2. Characteristics of T carries with/without periodontitis

	FcgRIIB-nt232T		
	Periodontitis (n = 13)	**Non-periodontitis (n = 48)**	***P*-value**
Gestational age at delivery (weeks)	36.68 ± 3.56	40.12 ± 4.73	0.5442
Maternal age (years)	42.18 ± 4.03	39.35 ± 4.15	0.1081
SBP at the third trimester	136.12 ± 8.07	119.71 ± 14.55	0.0106*
DBP at the third trimester	82.44 ± 4.98	73.89 ± 11.07	0.0193*
SBP after delivery	132.31 ± 14.54	127.90 ± 12.86	0.4657
DBP after delivery	81.50 ± 10.70	76.97 ± 9.64	0.2547

The *FcgRIIB*-nt232I/T polymorphism was associated with periodontitis (P = 0.0319) and PIH (P = 0.414) in Chinese pregnancy women. In the *FcgRIIB*-232T carriers group, periodontitis was significantly associated with PIH (P = 0.0052). The percentage of periodontitis with *FcgRIIB*-232T carriers (T/I+TT) group was significantly higher than non-periodontitis with *FcgRIIB*-232T carriers (T/I+TT) group, periodontitis with *FcgRIIB*-232T non-carriers (II) group, non-periodontitis with *FcgRIIB*-232T non-carriers (II) group in **Table 3**. The significant higher percentage in PIH with *FcgRIIB*-232T carriers (T/I+TT) group was observed compared with T non-carriers group (P = 0.0414) in **Table 3**. The percentage of periodontitis with PIH in the *FcgRIIB*-232T carriers (T/I+TT) group was the highest in all the groups (P = 0.0052) in **Table 4**. The expression of level of *FcgRIIb* on peripheral B lymphocytes with *FcgRIIB*-232T carriers of Chinese pregnant women were significantly higher than in non-carriers, as shown in **Figure 1**.

Table 3. Association between *FcγRIIB*-nt232-I/T genotypes and status(periodontitis/PIH)

	T/I (n = 11)	**TT (n = 50)**	**II (n = 26)**	χ^2	***P*-value**
Periodontitis	3 (21%)	10 (72%)	1 (7%)	6.890	0.0319*
Non-Periodontitis	8 (12%)	40 (55%)	25 (33%)		
PIH	5 (29%)	11 (65%)	1 (6%)	21.672	0.0414*
Non-PIH	6 (8%)	39 (56%)	25 (36%)		

*P-value < 0.05.

Table 4. Periodontitis-PIH comorbidity in *FcγRIIB*-232T carries

	Periodontitis (n = 13)	**Non-periodontitis (n = 48)**	χ^2	***P*-value**
PIH	12 (86%)	2 (14%)	18.471	0.0052*
Non-PIH	1 (2%)	46 (98%)		

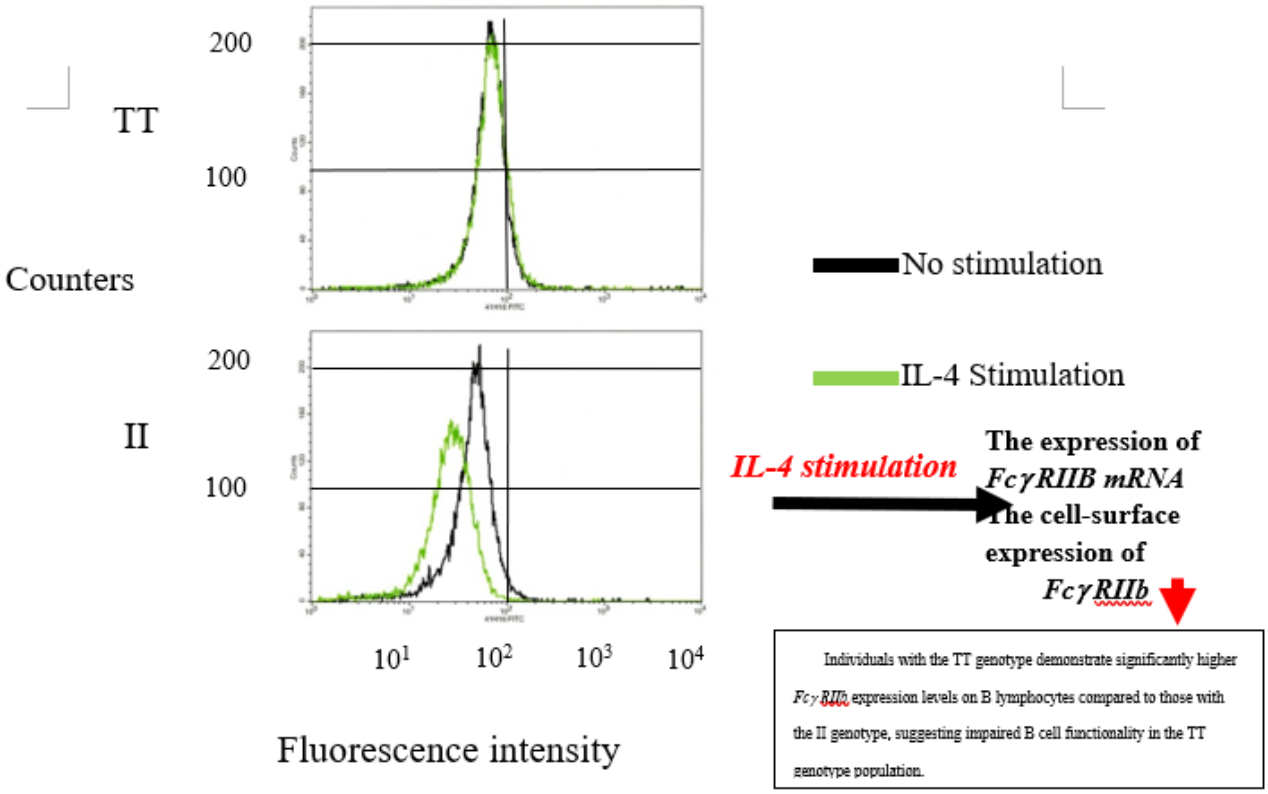

Figure 1. FcγRIIb expression levels on B lymphocytes across FcγRIIB-232I / T genotypes.

4. Discussion

Emerging evidence highlights the immunomodulatory effects of periodontal pathogens, particularly *Porphyromonas gingivalis*, on host immune regulation [18–20]. Clinical investigations demonstrate enhanced humoral immune responses in periodontitis-affected individuals, manifested by elevated serum IgG titers targeting the 40-kDa outer membrane antigen of *P. gingivalis* compared to healthy counterparts. Central to this immunological interplay *FcγRIIb*, a critical inhibitory receptor governing B-cell activation thresholds through its co-ligation with antigen-specific B-cell receptors via immune complexes, thereby modulating antibody-mediated feedback regulation [16]. Murine models of autoimmune disorders reveal that allelic variants of this receptor correlating with diminished surface expression predispose to pathogenic autoantibody production through impaired immune complex clearance [21]. The study extends these mechanistic insights to human periodontal disease pathogenesis. The observed enrichment of the *FcgRIIB*-232T allele (exon5) in aggressive periodontitis cohorts suggests a genotype-phenotype correlation, potentially mediated through attenuated IgG responsiveness to periodontal pathogens. Specifically, this allelic variant demonstrates reduced opsonophagocytic capacity against *P. gingivalis* antigens in chronic periodontitis patients. The study proposes that *FcgRIIB* polymorphisms may establish a proinflammatory microenvironment through two synergistic pathways: (1) Compromised pathogen clearance due to suboptimal IgG-mediated bacterial neutralization; (2) Dysregulated B-cell activation thresholds resulting in amplified inflammatory cytokine cascades [16]. However, the objects of these studies were not pregnant women. In this paper, the study first finds that there is a higher

prevalence of periodontitis in the *FcgRIIB*-232T carriers group compared with the T non-carriers group in Chinese pregnant women in **Table 1**, and the percentage of periodontitis with *FcgRIIB*-232T carriers (T/I+TT) group was significantly highest in all groups in **Table 3**. These results suggest that the *FcγRIIb*-232T allele of Chinese pregnant women is more susceptible to periodontitis than *FcγRIIb*-232I allele of Chinese pregnant women.

Infections play a significant role in spontaneous preterm labor and birth as well as in related neonatal complications [22]. The study's prior work established that the association of the 232T allele and the nt645+25AA genotype carriers with periodontitis might be related to the lower levels of IgG antibody response to *P. gingivalis* [15,16]. Our longitudinal investigations revealed a significant pathophysiological association between attenuated humoral responses to periodontal pathogens during first-trimester gestation and subsequent gestational complications. Specifically, diminished pathogen-specific immunoglobulin G (IgG) titers targeting *Porphyromonas gingivalis* in early pregnancy correlated with increased incidence of fetal growth restriction and spontaneous preterm delivery. Complementing these findings, functional genomics analyses have established the *FcγRIIB*-nt645+25A/G allelic variant as a predisposing factor for obstetric complications, demonstrating significant associations with premature rupture of membranes, early-onset preeclampsia, and preterm labor in maternal cohorts with periodontal infections [11,13]. In this paper, the *FcγRIIb*-232T allele of Chinese pregnant women is more susceptible to higher levels of SBP and DBP at the third trimester compared with the *FcγRIIb*-232I allele of Chinese pregnant women in **Table 1**, meanwhile, the significant higher percentage in PIH with *FcgRIIB*-232T carriers (T/I+TT) group was observed compared with T non-carriers group in **Table 3** also have been found. However, the significantly higher level of SBP and DBP after delivery has not been observed in this paper. Therefore, pregnancy is the main cause of these different results.

One limitation of this study is that the number of women with periodontitis and PIH with *FcgRIIB*-232T non-carriers is too less to difficult to statistical analysis; therefore, the study only analyzed the relationship between periodontitis and PIH in the *FcgRIIB*-232T carriers group in **Table 2** and **Table 4**. The study also finds that periodontitis in Chinese pregnant women is more susceptible to levels of SBP and DBP at the third trimester compared with non-periodontitis, and the percentage of periodontitis with PIH is the highest in all of the *FcgRIIB*-232T carriers groups. These results suggest that *FcgRIIB*-232T allele carriers of Chinese pregnant women are more susceptible to periodontitis and PIH, and periodontitis with *FcgRIIB*-232T allele carriers of Chinese pregnant women are more susceptible to PIH. However, the clinical periodontal parameters have not been found to associate with *FcgRIIB*-232I/T polymorphism. The observed inter-study variations likely stem from population heterogeneity in obstetric history profiles and differential gradients of periodontal disease progression, parameters that were systematically quantified in our longitudinal cohort analyses [23].

To understand the mechanism of these associations, we get peripheral blood from 3 *FcgRIIB*-232T non-carriers and 7T carriers of Chinese pregnant women, and determine the expression levels of *FcgRIIb* on peripheral B lymphocytes. The higher levels of *FcgRIIb* with T allele carriers are observed compared with the T allele non-carriers, but the result is not significant. This result suggests that the function of B lymphocytes with *FcgRIIB*-232T carriers of Chinese pregnant women may be weaker than non-carriers. This study did not test the IgG level response to periodontal bacteria and the level of maternal proinflammatory cytokines, therefore, it remains unclear whether adverse pregnancy outcomes are caused by *FcγRIIb* gene polymorphism-related inflammation, triggered by periodontal infection via increased proinflammatory cytokine levels. Further studies should validate this etiological hypothesis.

5. Conclusion

FcγRIIB-232T allele carriers of Chinese pregnant women are more susceptible to periodontitis and PIH, and periodontitis with *FcγRIIB*-232T allele carriers of Chinese pregnant women are more susceptible to PIH.

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The authors declare no conflict of interest.

Authors contribution

Study design: Yanming Wang and Xiaoqing Wang
Data collection: Baiqiang Xu and Xiaonan Wang
Data analysis: Junqiang Shan and Jiayu Fan
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