



## Original Article

# The Correlation between CYP2R1 rs10741657 and CYP27B1 rs10877012 Gene Polymorphism with the Incidence of Latent Tuberculosis Infection on Pregnant Mothers with Vitamin D Deficiency

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## ABSTRACT

**Background:** Vitamin D levels are affected by several vitamin D metabolism gene. The genetic variations of vitamin D metabolism gene, such as the CYP gene, plays a role in the first and the second vitamin D hydroxylation pathway, in which this will affect the levels of vitamin D serum. Low levels of vitamin D can play a role in the risk development of chronic infection diseases, and even malignancy; one of the aforementioned infections is the *M. tuberculosis* infection, so that on pregnant with LTBI are at a higher risk of developing into an active TB infection, especially if they are experiencing vitamin D deficiency.

**Methods:** The design used in this study is a case control study that follows 84 pregnant mothers on their third trimester from three hospitals in Medan, North Sumatera. The subject of this study is 42 pregnant mothers with LTBI and 42 pregnant mothers without LTBI. This study was conducted throughout December 2021 until July 2022. The assessed parameters are the IGRA and the vitamin D levels on pregnant mothers, which then will be further correlated with the CYP2R1 rs10741657 and CYP27B1 rs10877012 gene polymorphism. Further analysis utilized the Chi-squared test and the Fisher test.

**Results:** This study reported that 42,85% pregnant mothers with LTBI experienced vitamin D deficiency. This study also reported that there is not a significant correlation between CYP2R1 rs10741657 and CYP27B1 rs10877012 gene polymorphism and vitamin D levels ( $p = 0.541$  and  $0.057$ ), and there is not a signification correlation between CYP2R1 rs10741657 and CYP27B1 rs10877012 gene polymorphism and the incidence of LTBI ( $p = 0.03$ ;  $p = 0.001$ ).

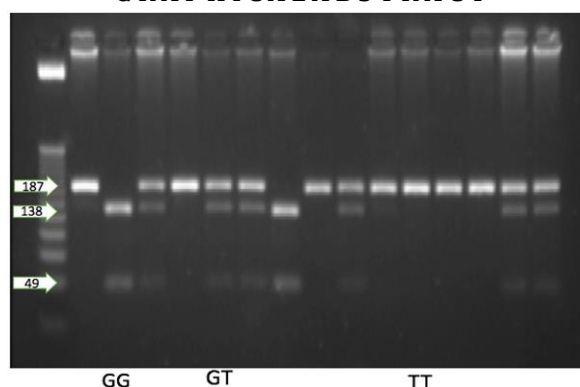
**Conclusions:** There is no signification correlation between CYP2R1 rs10741657 and CYP27B1 rs10877012 gene polymorphism on the incidence of LTBI and the vitamin D levels on pregnant with LTBI.

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## GRAPHICAL ABSTRACT



## Introduction

Latent tuberculosis infection has affected around 900 million women throughout the world [1], where it is estimated that there are as much as 216,500 cases of latent TB infection per year [2]. Latent TB infection during pregnancy has a high risk of developing into an active TB infection. This risk development relies on the immune system of the body [3] and the immune system mechanism is affected by the vitamin D levels. Low vitamin D levels can be found on people who are infected with *M. tuberculosis*, where a prior meta-analysis study reported that children who are infected with TB has a lower vitamin D levels compared to healthy children [4], and the deficiency of vitamin D is correlated with LTBI progressivity into becoming TB [5]. Meanwhile, deficiency, or even insufficiency of vitamin D can be found in around 1 billion people throughout the world [6, 7] and in Indonesia, around 95% out of 148 adult women suffers from deficiency and insufficiency of vitamin D [6].

Genetic variance on the genes involved in the vitamin D metabolism will affect the levels and function of vitamin D in the body. The decrease in 25(OH)D serum can occur, despite only having a genetic mutation on one base [8]. A study by *Genome-wide Association Studies* (GWAS) reported that the genes playing a role with the vitamin D metabolism are GC (vitamin D binding protein), CYP24A1, CYP2R1, and DHCR7 in relation to the vitamin D levels and Vitamin D

Receptor (VDR), CYP27A1, and CYP27B1, which correlations to the vitamin D metabolic pathway. The study from GWAS reported that GC, CYP2R1, DHCR7, and VDR are correlated with low vitamin D levels [9].

Genetic variance on vitamin D metabolism gene, aside from affecting the levels of vitamin D serum, can also play a role in the risk development of a chronic infection, and even malignancy. In a systematic review study, it was reported that CYP2R1 rs10741657 and CYP27B1 rs10877012 polymorphism has a significant correlation with vitamin D [10, 11]. Other research has also reported that CYP2R1 and CYP27B1 polymorphism, which are the metabolic enzyme of vitamin D, can affect the vitamin D levels, and play a role in chronic diseases such as TB, and even malignancy [12, 13].

## Materials and Methods

### Study design

This was a case-control study. The participants of this study were 84 pregnant mothers (42 case groups and 42 control groups). The subjects were categorized based on their diagnosis of LTBI or non-LTBI. The collected data included IGRA testing results, vitamin D levels, and CYP2R1 rs10741657 and CYP27B1 rs10877012 polymorphism genes from pregnant mothers in their third trimester of pregnancy, starting from December 2021 until July 2022.

The subjects for this study originated from three hospitals in Medan, North Sumatera, where the subjects were pregnant mothers who routinely underwent prenatal check-ups in research hospitals. This study was conducted directly on the subjects after they agreed to participate and signed an informed consent form. Prior to sign the informed consent form, the participants were given an oral explanation.

#### *Participant*

Sampling in this study used consecutive sampling method, where subjects who met the inclusion and exclusion criteria would be selected as research subjects. The inclusion criteria were pregnant women in the third trimester of pregnancy without complications. Pregnant women with pregnancy complications (hypertension, eclampsia, and DM) and pregnant women diagnosed with COVID-19 were included as exclusion criteria. All subjects in this study received vitamin D supplements of 1000 IU daily for one month from their obstetricians.

#### *Statistical analysis*

The chi square test or fisher exact test was used to analyze the correlation between CYP2R1 rs10741657 and CYP27B1 rs10877012 gene polymorphisms and vitamin D and ILTB levels (IGRA positive). The significance value was below 0.05 ( $p < 0.05$ ).

#### *Examination*

All examinations for this study were carried out at the Integrated Laboratory of the Faculty of Medicine, University of North Sumatera. Each measurement was performed twice, and the obtained data was the average of measurement results. Blood samples from pregnant women were obtained through the medial cubital vein in the left or right arm, during the third trimester of pregnancy before delivery. Blood samples from the newborn's umbilical cord were taken at the time of delivery. IGRA testing was performed to categorize the case and control groups by Enzyme-linked Immunosorbent Spot Assay (ELISPOT) by assessing the number of spots that appeared on the incubated specimen. The results

were read under microscopic view, and if there were  $\leq 5$  spots that appeared, it was classified as IGRA-negative, and  $\geq 6$  spots that appeared were classified as IGRA-positive. Vitamin D testing was performed by assessing serum vitamin D levels in mothers and infants by ELISA test, using an Enzyme Linked Analysis Techniques Immunosorbent Assay (ELISA) kit (DiaSorin, USA), with classification of vitamin D (25-hydroxy vitamin D) (25(OH)D3) levels in pregnant women as follows: Normal Maternal Level:  $> 30$  ng/mL, Insufficient Maternal Level: 21-29 ng/mL, and Insufficient Maternal Level:  $< 20$  ng/mL.

The CYP2R1 rs10741657 polymorphism gene testing was conducted on pregnant mothers. The initial step is the DNA isolation from the venous blood with the forward primer CYP2R1 5'-GGGAAGAGCAATGACATGGA-3' and the reverse primer CYP2R1 5'-GCCCTGGAAGACTCATTG-3. The CYP2R1 PCR cycle is initial denaturation at 94 °C for 5 minutes, denaturation at 94 °C for 30 seconds, annealing at 57 °C for 30 seconds, extension at 72 °C for 40 seconds, and the final extension at 72 °C for 7 minutes. On the CYP27B1 rs10877012 testing, the DNA isolation were done using the forward primer CYP27B1 5'-GCCTGTAGTGCTTGAGAGG-3' and the reverse primer CYP27B1 5'-CAGTGGGGAATGAGGGAGT-3'. The CYP27B1 PCR cycle is initial denaturation at 95 °C for 5 minutes, denaturation at 95 °C for 30 seconds, annealing at 60 °C for 30 seconds, extension at 72 °C for 60 seconds, and final extension at 72 °C for 10 minutes. The next step is to conduct the PCR restriction length polymorphism (RFLP) testing, which utilized the MN1 enzyme as the restriction enzyme for CYP2R1 rs10741657, with the electrophoresis pattern showing homozygous GG genotype (151bp, 105bp, 32 bp), AA (256bp, 32bp), and heterozygous GA (256 bp, 151bp, 105bp, 32bp). On the PCR RFLP for the CYP27B1 rs10877012 gene, the HINFL enzyme was utilized as the restriction enzyme, with the electrophoresis pattern showing homozygous GG genotype (138bp, 49bp), TT (187bp), and heterozygous GT (187bp, 138bp, 49bp).

*Ethics approval and consent to participate*

This study received ethical approval based on the Declaration of Helsinki guidelines. All research subjects involved read and were given an explanation of the study. All research subjects understood and signed the consent. All research procedures have been ethically tested and approved by the Ethics Committee of the University of North Sumatra, no. 1012/KEPK/USU/2021, dated 8 October 2021.

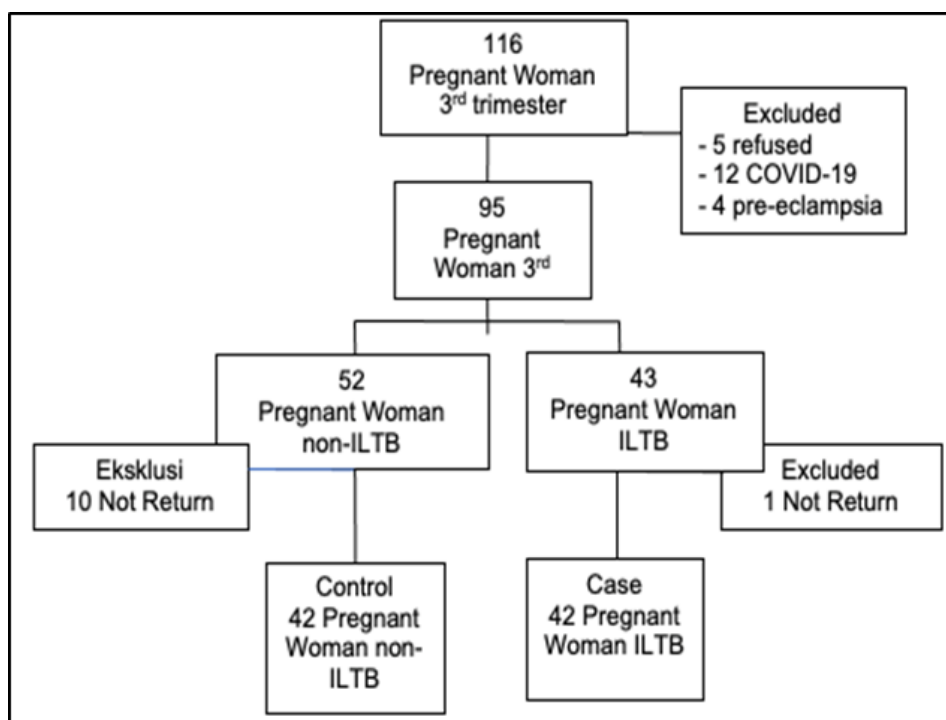
**Results and Discussion**

From the 84 participants, 42 pregnant mothers without LTBI (IGRA-negative) were categorized as the control group and 42 pregnant mothers with LTBI (IGRA-positive) were categorized as the case group (Figure 1).

The subjects for this study are pregnant mothers in their third trimester of pregnancy without any pregnancy complication that routinely did antenatal check-ups in research hospitals. In this study, the number of adult pregnant mothers were 82 people, and young adult pregnant mothers were 2 people. The largest amounts of pregnant mothers that were of Javanese descent

consisted of 28 out of 84 people. 47 pregnant mothers worked as a housewife, 16 people worked as an employee at a state-owned company (SOEs) or as a civil servant, 8 people were self-employed, and 5 people worked at a privately-owned company. 59 mothers had a Bachelor’s Degree as their most recent education background, 12 people had an Associate’s Degree, 9 people had a High School Diploma, and 4 people had a Master’s Degree (Table 1).

The levels of vitamin D were classified into: deficiency (below 20 ng/mL), insufficiency (21-29 ng/mL), and normal (30-100 ng/mL). In this study, out of 84 pregnant mothers, 4 suffered from vitamin D deficiency (4.7%), 23 suffered from vitamin D insufficiency (26.2%), and 58 mothers had normal levels of vitamin D (69.1%). Out of all the pregnant mothers that suffered from either deficiency or insufficiency of vitamin D, 10 mothers were housewives, 7 people were employees at an SOE or worked as a civil servant, and 4 people were self-employed. Despite this, out of all of the pregnant mothers with normal vitamin D levels, the largest amount of occupation in this group were housewives, with 36 people (Table 2).



**Figure 1:** Study sample

**Table 1:** Data characteristics of ILTB pregnant women and non-ILTB pregnant women

Parameter	Group	
	ILTB (n=42), n(%)	Non-ILTB (n=42), n(%)
Age (year)		
Young adults (18-24)	1 (50)	1 (50)
Adult (25-44)	41 (50)	41 (50)
Ethnic group		
Bataknese	12(54.5)	10(45.5)
Minang	4(28.6)	10(71.4)
Javanese	17(60.7)	11(39.3)
Aceh	2(50)	2(50)
Chinese	3(27.3)	8(72.7)
Malay	2(66.7)	1(33.3)
Bugis	2(100)	0(0)
Occupation		
Self-employed	5(62.5)	3(37.5)
Public employees	8(57.1)	6(42.9)
Private employees	2(40)	3(60)
Health workers	3(30)	7(70)
Housewife	24(51)	23(49)
Education		
SMA	7(77.8)	2(22.2)
D3	6(50)	6(50)
S1	26(44.1)	33(55.9)
S2	3(75)	1(25)

**Table 2:** Classification of vitamin D levels of pregnant women based on occupation

Occupation	Vitamin D Levels		
	Deficiency, n(%)	Insufficiency, n(%)	Normal, n(%)
Pregnant Woman ILTB (42)			
Self-employed	1 (20)	3 (60)	1 (20)
Public employees	2 (25)	4 (50)	2 (25)
Private employees	0 (0)	1 (50)	1 (50)
Health workers	0 (0)	1 (33.3)	2 (66.7)
Housewife	1 (4.2)	5 (20.8)	18 (75)
Pregnant Woman non-ILTB (42)			
Self-employed	0 (0)	0 (0)	3 (100)
Public employees	0 (0)	1 (16.7)	5 (83.3)
Private employees	0 (0)	1 (33.3)	2 (66.7)
Health workers	0 (0)	2 (25)	5 (75)
Housewife	0(0)	5 (21.7)	18 (78.3)
Total	4 (4.7)	23 (27.3)	57 (68)

The PCR electrophoresis results from the DNA isolate of the cytochrome gene CYP2R1 rs10741657 shows the DNA strand with the genotype variant GG (151bp, 105bp, 32bp), AA (256bp, 32bp), and GA (256 bp, 151bp, 105bp, 32bp) (Figure 2) and the PCR electrophoresis

from the DNA isolate of the cytochrome gene CYP27B1 rs10877012 shows the DNA strand with the genotype variant GG (138bp, 49bp), TT (187bp), and GT (187bp, 138bp, 49bp) (Figure 3).

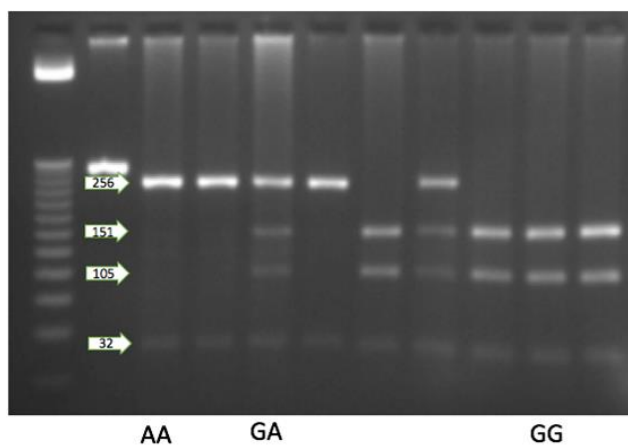


Figure 2: PCR-RFLP genotype CYP2R1

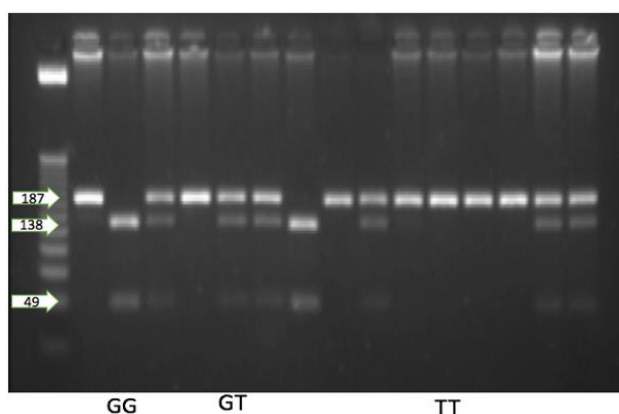


Figure 3: PCR-RFLP genotype CYP27B1

Table 3: Frequency distribution of gene polymorphisms in pregnant women

Genotype	Pregnant Woman ILTB (n,%)	Pregnant Woman non-ILTB (n,%)	P-value
CYP2R1 rs10741657			
GG	15 (35.7)	16 (38.1)	1.000
GA	16 (38.1)	17 (40.5)	
AA	11 (21.4)	9 (21.4)	
CYP27B1 rs10877012			
GG	9 (21.4)	12 (28.6)	0.604
GT	28 (66.7)	18 (42.9)	
TT	5 (11.9)	12 (28.1)	

Kolmogorov-Smirnov test.

Table 4: The average value of vitamin D levels in genotype variants in pregnant women

Varian genotype	Frequency (n)	Average of vitamin D (ng/mL)	P-value
CYP2R1 rs10741657			
GG	31	43.78 ± 29.17	0.871
GA	33	44.34 ± 27.11	
AA	20	58.90 ± 59.19	
CYP27B1 rs10877012			
GG	21	46.61 ± 24.13	0.187
GT	46	52.87 ± 47.31	
TT	17	34.55 ± 12.12	

The polymorphism type for CYP2R1 rs10741657 and CYP27B1 rs10877012 were tested with Hardy-Weinberg Equilibrium (HWE) and a p-value of  $> 0.05$  were obtained, which shows that this polymorphism is disequilibrium, so that the frequency of allele distribution in CYP2R1 and CYP27B1 were consistent with the HWE principle. On the CYP2R1 rs10741657, the frequency distribution of the GA heterozygous genotype variant was the largest variant found in LTBI pregnant mothers (38.1%) and non-LTBI pregnant mothers (40.5%). On the CYP27B1 rs10877012, the frequency distribution of the GT heterozygous genotype variant was the largest one found in LTBI pregnant mothers (66.7%) and non-LTBI pregnant mothers (42.9%) (Table 3). On the polymorphism of CYP2R1 rs10741657, the highest mean value of vitamin D levels on pregnant mothers were found in the AA genotype, and the lowest mean value were found in the GA genotype, with a statistically

insignificant difference ( $p = 0.871, p > 0.05$ ). On the polymorphism of CYP27B1 rs10877012, the highest mean value of vitamin D levels on pregnant mothers were found in the GT genotype, and the lowest mean value were found in the TT genotype, with a statistically insignificant difference ( $p = 0.187, p > 0.05$ ) (Table 4).

On the analysis of the correlation between genotype with vitamin D levels of pregnant mothers based on their LTBI status, the vitamin D levels on 42 pregnant mothers with LTBI-with the CYP2R1 rs10741657 polymorphism variance-the highest amount of genotype was the AA genotype, and the lowest genotype was the GG genotype ( $p = 0.903$ ). Meanwhile, the mean value of vitamin D on 42 non-LTBI pregnant mothers, the highest amount of genotype was also the AA genotype, but the lowest amount of vitamin D levels on non-LTBI pregnant mothers were found on pregnant mothers with the GA genotype ( $p > 0.378$ , Table 5).

**Table 5:** Differences in mean vitamin D based on genotype in pregnant women

Genotype	Average of vitamin D in Pregnant Woman ILTB ng/mL (frekuensi)	P-value	Average of vitamin D in Pregnant Woman non-ILTB ng/mL (frekuensi)	P-value
CYP2R1 rs10741657				
GG	40.55 ± 20.46 (15)	0.903	46.80 ± 35.94 (16)	0.378
GA	43.64 ± 27.97 (16)		44.99 ± 27.12 (17)	
AA	63.35 ± 77.28 (11)		53.47 ± 28.01 (9)	
CYP27B1 rs10877012				
GG	44.36 ± 19.21 (9)	0.256	48.31 ± 27.98 (12)	0.386
GT	52.25 ± 52.82 (28)		53.83 ± 38.62 (18)	
TT	28.20 ± 6.40 (5)		37.19 ± 13.14 (12)	

**Table 6:** Relationship between gene polymorphism and vitamin D levels in pregnant women

Genotype	Mother's level of vitamin D		OR	IK95% (LL-UL)	P-value
	Low (<30)	Normal (30-100)			
CYP2R1 rs10741657					
GG+GA	24(37.5)	40(62.5)	1.400	0.474-4.131	0.541
AA	6(30)	14(70)			
CYP27B1 rs10877012					
GG+GT	21(30.9)	47(69.1)	0.348	0.114-	0.057
TT	9(56.3)	7(43.8)		1.058	

Chi-square test.

Further analysis to determine the correlation between the G allele polymorphism on the CYP2R1 rs10741657 gene with the vitamin D levels on 84 pregnant mothers showed an OR value of OR = 1,400 (CI 95%: 0.474-4.131) with a *p*-value of 0.541 (*p* > 0.05), and the correlation between the G allele polymorphism on the CYP27B1 rs10877012 gene with the levels of vitamin D on 84 pregnant mothers showed an OR value of OR = 0.384 (CI 95%: 0.114 - 1.058) with a *p*-value of 0.057 (*p* > 0.05). These results showed that there is no statistically significant correlation between the G allele polymorphism on the CYP2R1 rs10741657 and CYP27B1 rs10877012 gene with the vitamin D levels in pregnant mothers (Table 6).

The correlation analysis between the G allele polymorphism in the CYP2R1 rs10741657 gene on the incidence of ILTB showed an OR value of OR = 0.769 (CI 95%: 0.280- 2.106) with a *p*-value of 0.798 (*p* > 0.05). The correlation analysis between the G allele polymorphism in the CYP27B1 rs10877012 gene on the incidence of ILTB showed an OR value of 2.90 (CI 95%: 0.983 - 9.339) with a *p*-value of 0.101 (*p* > 0.05). This result showed that the G allele in CYP2R1 rs10741657 and CYP27B1 rs10877012 gene on pregnant mothers does not increase the risk of a latent TB infection (Table 7).

The IGRA screening on pregnant mothers during their gestation in Indonesia has not been done routinely, even on areas with a high TB incidence number. In this study, when we conducted the LTBI screening test, we found that 45.3% out of 95 pregnant mothers on their third trimester were pregnant mothers with LTBI. This number

is higher than the study conducted in Sudan, on 2019, where the study reported that 18% of pregnant mothers included in their study were pregnant mothers with LTBI [14], and in a 2021 study in Uganda, where the study reported that 38% of pregnant mothers included in their study were pregnant mothers with LTBI [15]. Based on previous studies [14, 15], the results reported in this study showed an increase of LTBI pregnant mothers incidences compared to previous years. Despite these increases were reported from various areas, this results still showed that in the place of this study, which is Medan, North Sumatera, had sufficiently high LTBI incidence on pregnant mothers.

In this study, each of the pregnant mothers was in healthy condition, even on pregnant mothers with LTBI. This is in accordance with prior research where it was reported that a person with LTBI will not show any clinical signs found in tuberculosis, and might even have a normal thorax radiographic image [16, 17].

In this study, 32.1% out of 84 pregnant mothers suffered from deficiency to insufficiency of vitamin D. This result is different from the reported results of a study conducted in West Sumatera, where the study reported that 66.6% out of 60 pregnant mothers had low levels of vitamin D [18], and in several other countries, on a meta-analysis study, it was reported that pregnant mothers who had vitamin D levels that were below 25 ng/mL were found in America (9%), Europe (23%), Eastern Mediterranean (79%), South East Asia (87%), and West Pacific (13%) [19].

**Table 7:** Relationship of gene polymorphisms to the incidence of latent tuberculosis infection

Genotype	Group		OR	IK95% (LL-UL)	P-value
	ILTB	Non-ILTB			
CYP2R1 rs10741657					
GG+GA	31(73.8)	33(78.6)	0.769	0.280-2.106	0.798
AA	11(26.2)	9(21.4)			
CYP27B1 rs10877012					
GG+GT	37 (88.1)	30(71.4)	2.960	0.938-	0.101
TT	5 (11.9)	12(28.6)		9.339	

*Chi-square test.*



The percentage difference on pregnant mothers that suffers from vitamin D deficiency on these different areas is in accordance with several previous studies reported the factors that influence the vitamin D levels on pregnant mothers are domicile environment, sun exposure, vitamin D intake, and bacterial infection process [20-24].

In this research, the most common frequency distribution for the heterozygous genotype was the GA genotype, with 33 people (39.3%), and the least common genotype was the AA genotype with 20 people (23.8%). This result is in accordance with a study on healthy individuals in Denmark, and a study on unhealthy individuals in Jordan, Serbia, and Chennai (India), where the GA genotype of CYP2R1 rs10741657 was the largest genotype amount that was reported, but it was not in accordance with a study with healthy subjects in Singapore, Jordan, and Bangladesh, that reported the GG genotype in CYP2R2 rs10741657 was the largest that was reported [25-30]. The difference in the genotype differences can be attributed due to the variance in the continent of origins, country of origins, and the population's race. The most common frequency distribution for the heterozygous type of CYP27B1 rs10877012 was the GT genotype, with 46 people (54.8%), and the least common heterozygous genotype was the TT genotype, with (20.2%). This result is in accordance with a prior study in Poland where the study reported that the largest found amount of genotype was the GT genotype (44%) out of 325 people, and this result is different from a prior study in Brazil and Mexico where in the CYP27B1 rs10877012, the study reported that they found the GG genotype to be the most common genotype that was found [31].

This study had some limitations, including the early detection of LTBI conducted at the end of the third trimester of pregnancy, where it should have been done since the start of the pregnancy, especially since the researchers noticed an increase in LTBI prevalence compared to last year's prevalence numbers. Interviews and assessments towards several risk factors that could affect the vitamin D levels, such as natural

food intake and length of sunlight exposure on mothers during pregnancy, was not conducted by the researchers. This can be conducted in future studies to obtain a more comprehensive assessment. Other vitamin D metabolism gene testing aside from CYP2R1 rs10741657 and CYP27B1 rs10877012 was not conducted, and this can be done in future research as well. The long-term monitoring on pregnant mothers with LTBI towards the administration of Tuberculosis Preventive Treatment (TPT) and the LTBI development into TB should be conducted in future studies, due to the mothers will be afflicted with LTBI for their entire life.

## Conclusion

The polymorphism of CYP2R1 rs10741657 and CYP27B1 rs10877012 does not play a role towards the incidence of LTBI on pregnant mothers with LTBI. The polymorphism of CYP2R1 rs10741657 and CYP27B1 rs10877012 did not play a role towards the vitamin D levels on pregnant mothers with LTBI, but the number of pregnant mothers with LTBI with vitamin D deficiency was larger than non-LTBI pregnant mothers.

## Conflict of Interest

No potential conflict of interest was reported by the authors.

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## Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

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