Association of Mothers' Single Nucleotide Polymorphism of Vitamin D Receptor's FokI Gene with Risk of Preterm Birth and Birth Weight: A Review

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Declaration

It is hereby declared that

1. The thesis submitted is my/our own original work while completing degree at BRAC University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
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Approval

The thesis/project titled "Association of mothers single nucleotide polymorphism of vitamin D receptor's FokI gene with risk of preterm birth and birthweight: A review" submitted by Umme Habiba of Summer, 2022 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Hons.).

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Ethics Statement

This study does not include any animals or human trails.

Abstract

Preterm birth and lower birth weight are one of the notable adverse effects of pregnancy. Recent studies have found the association of maternal vitamin D receptor gene's polymorphism in one nucleotide with these events. Contributing genes for these factors are ApaI, BsmI, FokI, and TaqI. FokI gene has shown the most correlation among these genes with preterm birth. Nevertheless, in this study, we did not find any association of birth weight with FokI gene's polymorphism of maternal vitamin D receptor. There are many researches focused on this genotypic change, however, all of them are conducted on a specific ethnicity. This subject needs more research to exhibit the exact correlation.

Keywords: Maternal vitamin D single nucleotide polymorphism; FokI; Preterm; Birthweight; Low birth weight.

Dedication

Dedicated to all the mothers who struggle with adverse outcomes of pregnancy.

Acknowledgement

At the very beginning, I would like to thank Almighty Allah, who is the source of my strength.

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SNP	Single Nucleotide Polymorphism
VDR	Vitamin D Receptor
LBW	Low Birth Weight
DNA	Deoxyribonucleic Acid
PTB	Preterm Birth

Chapter 1

Introduction

If a gestational age of less than 37 weeks results in a new birth, it is defined as preterm birth (PTB). Every year globally 15 million preterm infants are taking birth which makes it one of the major public health concerns (Quinn et al., 2016) . After an infant is born, with in an hour before notable postnatal weight loss, the measured body weight of the infant is defined as the first weight. On that condition, the first body weight being less than 2500 grams (2499 grams id included) is marked as low birth weight, according to World Health Organization (WHO) (Quinn et al., 2016) .

Both preterm birth and low birth weight are associated with neonatal deaths. In the year of 2010, 1 in every 10 infants were born premature in Bangladesh (Shah et al., 2014) Being a least developed country, where most of the population are deprived of advanced healthcare system about 17.02% infants died due to preterm birth alone in year 2018-19 (Indicators, 2019). Among the newborns the prevalence of low birth weight was found to be 19.9% which also showed very low discrimination of economic status of the mother as a variant (Khan et al., 2020).

Vitamins are one of crucial elements needed for the body and its deficiency can lead to serious adverse effects in the body (Smart, 1999). There are 13 different types of them such as vitamin A, D, E, K which are fat soluble, on the other hand vitamin B, C are water soluble (Semba, 2012). Vitamin execute major physiological functions in our body such as: metabolism, boosting our immunity, growth, vision, reproduction, absorption of various minerals and many others (Godoy-Parejo et al., 2020). Vitamin D is one the fat-soluble vitamins and plays a significant role in our body (Health, 1989).

Ergocalciferol (vitamin D_2) and cholecalciferol (vitamin D_3) are two prohormones of vitamin D. Vertebrates are dependent on inter-vertebrates as well as fungi as they can produce vitamin D_2 (O'Mahony et al., 2011). On the other hand, from cholesterol we get 7-dehydrocholestrol which is the precursor of vitamin D_3. Human skin on the exposure of the ultraviolet (UV) radiation converts 7-dehydrocholestrol to vitamin D_3 (Kato, 2000b). These two prohormones when being present on biological system turns into the active form of vitamin D which is 1,25-dihydroxyvitamin D (calcitriol) (O'Mahony et al., 2011, Holick, 2016).

The absorption of vitamin D and its expression is dependent on vitamin D and vitamin D receptor (VDR) binding. VDR is a member of nuclear hormone super family and upon binding to vitamin D it then exerts critical role such as gene expression and immunological function modulation, prevention against diseases and others (Mangelsdorf,' et al., 1995) . The activity of vitamin D is controlled by vitamin D receptor, also mentioned as Nr1I1 or calcitriol receptor. The active form of vitamin D acts as a ligand to the receptor, and therefore, ligand binding to the VDR gives off the anticipated results (Kato, 2000a). However, even after ingesting sufficient amount of vitamin D we often observe various vitamin D deficiency related adverse effects and recent data has shown there is association of VDR single nucleotide polymorphism with it (Li et al., 2021).

Genetic variation can lead to numerous negative effects in our body (Crider et al., 2005). Polymorphism in the DNA causes formation of more than one nucleotide base pairing at one particular point of the DNA. One of the notable genetic mutations is single nucleotide polymorphism. Recent studies have shown that vitamins together with their receptors play a major role in PTB and LBW. Genetic risk factors were noticeable for both PTB and LBW. Among those, vitamin D and vitamin D receptor gene variation have manifested potential co-relation (Barchitta et al., 2018). Single nucleotide polymorphism of FokI gene has the strongest interrelation (Kosik et al., 2020).

Single nucleotide polymorphisms (SNPs) are a point mutation in the DNA. They give rise to dissimilar alleles containing substituted bases at one position of a nucleotide in a locus (Keats & Sherman, 2013). Maternal variation of DNA has shown to be closely related with PTB and LBW (Sheikh et al., 2016).

1.1 Aim of This Study

The aim of this review is to cross-talk between FokI gene mutation specifically, single nucleotide polymorphisms (SNPs) of mother's vitamin D receptor and its contribution with preterm birth and low birth weight.

1.2 Objectives

- To underline the association of mother's vitamin D receptor's SNP of FokI gene in infant's low-birth weight.
- Establishing the correlation between preterm birth and mother's vitamin D receptor's SNP of FokI gene.
- Critically evaluating all the existing information to synthesize an appropriate interrelationship between mother's vitamin D receptor's SNP of FokI gene and LBW as well as PTB.

Chapter 2

Methodology

This study was conducted by reviewing Elsevier journals, Scopus databases for appropriate information, BMJ Open, PubMed, BMC Pediatrics, BMC Genomics, The Lancet. While searching for relevant information certain key words such as ‘preterm’, ‘Vitamin D’, ‘low-birth weight’, ‘FokI gene’, ‘Vitamin D receptor’, ‘single nucleotide polymorphism*’, ‘mother’s vitamin D receptor single nucleotide polymorphism*’ keywords were used for suitable articles. The review paper cross-talk between mother’s vitamin D receptor’s FokI gene’s association with preterm birth and low birth weight. All the information were retrieved manually and the study includes grey together with black literatures. The information sources were cited using Mendeley software.

Chapter 3

Vitamin D and Genetic Predisposing Factors Contributing to its Deficiency

The production of Vitamin D in the human body is associated with multilateral steps. In the figure 1, we can see that, in the human epidermis 7-dehydrocholesterol is present (Huynh, 2020). It is then broken down to an intermediate of cholecalciferol by exposure to UV-B rays from the sun. The formation of this product is dependent on the intensity of the UV-B ray coming from the sun and skin coloration (Holick et al., 1980). The heat that is present in the body causes the change of this intermediate to cholecalciferol (Arshad et al., 2022). From this substance, we obtain vitamin D. Vitamin D can be obtained directly from a dietary substance such as sea-fish rich in omega-3, plants, eggs, and fruits (Larqué et al., 2018). In the liver, the 25-hydroxylase enzyme converts vitamin D into 25-hydroxyvitamin D (Tieu et al., 2012). From there 1-α-hydroxylase in the kidney converts it to activated vitamin D or 1,25-dihydroxyvitamin D (Bikle et al., 1986). Vitamin D can also be deactivated by 24-hydroxylase (Jones et al., 2012). It can also go to the paracrine glands and exert its effect (Schuster, 2011). All of these result in the presence of vitamin D in the bloodstream. When vitamin D is present in the bloodstream of the mother, it goes to the placenta and modulates immunological attributes. And, finally, from the placenta, it goes to the fetus and helps in the vitamin D-regulated functions (Arshad et al., 2022).

The bioavailability of vitamin D is dependent on binding to its receptor. Many times, it has been evident that, despite consuming enough vitamin D, the serum concentration is not sufficient. Vitamin D deficiency in pregnancy can be associated with preeclampsia, low birthweight, and preterm birth (Baker et al., 2011; Leffelaar et al., 2010; TePoel et al., 2011; Zaki et al., 2017). Now we will look in to the genetic aspect related to vitamin D deficiency:

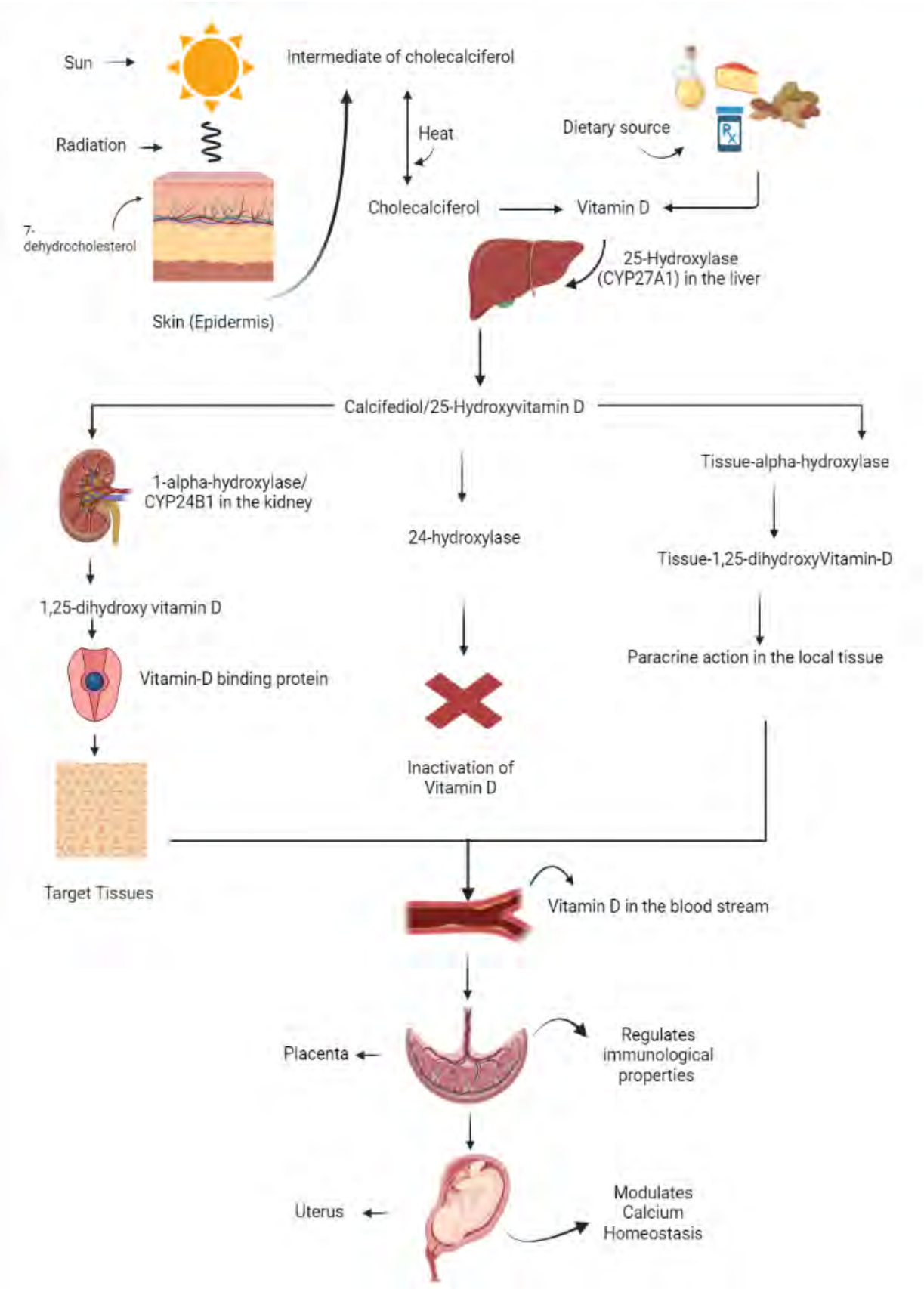

Figure 1: Formation and absorption of vitamin D in a pregnant mother's body

Table 1: VDR gene SNP affecting vitamin D concentration

Reference	Gene	Genotype	Vitamin D concentration <30 ng/ml	Vitamin D concentration ≥30 ng/ml	Ethnicity	*P*-value
(Divanoglou et al., 2021)	TaqI	TT	16	14	Greek	0.048*
		Tt	40	11		
		tt	13	4		
	FokI	FF	30	10		0.45
		Ff	31	13		
		ff	8	6		
	ApaI	AA	20	10		0.24
		Aa	38	11		
		aa	11	8		
	BsmI	BB	15	4		0.04**
		Bb	40	12		
		bb	14	13		

*Statistically significant *p*-value in comparison to various genotypes of TaqI gene

** Statistically significant *p*-value in comparison to various genotypes of BsmI gene

Table 1 states how genotypic change can affect vitamin D concentration. Here, the TaqI and BsmI genotypic change show a relation with vitamin D concentration in the body. This study includes both the male and female population. In respect of TT against Tt and tt allelic states the *p*-value is 0.048 which shows, the SNP of TaqI gene changes the vitamin D level in the body and can cause deficiency. BsmI gene also shows the same effect in respect to BB,Bb, and

bb allelic states. The *p*-value was 0.04, making BsmI gene's SNP a susceptible factor for low concentration of vitamin D in the body. However, FokI and ApaI gene doesn't show any relation with vitamin D concentration.

Here, as we see the correlation of VDR SNP and vitamin D deficiency, it is noteworthy mentioning, vitamin D deficiency is associated with Preterm birth, however, the meta-analysis also mentioned that insufficiency did not impact lower birth weight (Tous et al., 2020).

3.2 FokI Gene and Preterm birth

Preterm birth is one of the alarming global epidemiology (Vogel et al., 2018). 70% of the PTB ally with neonatal deaths (Goldenberg et al., 2008). Among the survived Preterm infants 75% face severe health conditions like respiratory syndromes, neurological disorders, cardiovascular diseases, adolescent diabetes, and cancer (Akre et al., 2006; Manzon et al., 2014b; Rotteveel et al., 2008). All these crucial factors contributed to discovering the mechanism of PTB of great interest to scientists and researchers.

After looking for the appropriate mechanisms, it was seen that mothers who have premature children, sometimes have more than one child as premature; they also have a familial foundation which indicates there can be a genetic predisposing factor associated with preterm births (Byrne & Morrison, 2002; Fiscella, 2005; Goldenberg et al., 2008; Menon et al., 2006; Ward et al., 2005). proved there is an association between the mother's VDR's SNPs association with PTB (Barchitta et al., 2018). PTB is not only associated with detrimental health conditions in infants, rather it brings tremendous emotional and economic pressure on the families (Manzon et al., 2014b). PTB is not associated with a single aspect rather it is a multi-factorial crisis; stress, educational level of the mother, occupation status, smoking habit, and many other pathophysiological conditions can contribute to it (Barchitta et al., 2018; Crider et al., 2005; Kramer et al., 2009; Michalowicz et al., 2009).

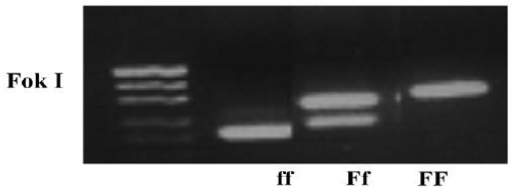

Figure 2: FokI gene's various polymorphic state; ff, Ff and FF allelic position (Source: Manzon et al., 2014b)

The VDR gene is composed of twelve exons and nine introns (*VDR: Chr12 - Genome Data Viewer - NCBI*,2023). They are found at chromosome 12q13.11 (Biswas et al., 2018; Ciéslińska et al., 2017; Groves et al., 2014; *VDR: Chr12 - Genome Data Viewer - NCBI*, 2023). The FokI, BsmI, TaqI, and ApaI genes are pointed to be causative to preterm birth because of single-point mutation (Kosik et al., 2020). A di-allelic polymorphism of FokI gene at C>T nucleotide (rs10735810) in the VDR is been found on the coding sequence; on the other hand, it has been also proved that FokI plays role in the defense mechanism of the body (Manzon et al., 2014b; van Etten et al., 2007). Another SNP of FokI gene is rs2228570 A>G, which has shown correlation with preterm birth in Brazilian ethnicity (Javorski et al., 2018).

Table 2: Allele and Genotyping periodicity of FokI gene's two polymorphic states in VDR among the mother's of preterm birth and full-term birth (Controlled group)

Reference	Gene	Genotype	Total cases of preterm birth	Controlled group number	Ethnicity	Allele	*P* values
(Manzon et al., 2014a)	rs10735810	C>T	62.5%	29.2%	Jewish and Arabs	FF, ff, Ff	0.0101*
(Javorski et al., 2018)	Among mothers' who previously had preterm births	C/C	35.6% (37)	55.3% (47)	Brazilian	-	0.218
		C/T-T/T	64.4% (67)	44.7% (38)			
		C/C-C/T	77% (80)	95.3% (81)			0.386
		T/T	23% (24)	4.7% (4)			
		C/C-T/T	58.7% (61)	60% (51)			0.536
	rs2228570	C/T	41.3% (43)	40% (34)			
	Preterm birth among multiparous mother's	C/C	35.6% (37)	55.3% (47)			0.697
		C/T-T/T	64.4% (67)	44.7% (38)			
		C/C-C/T	77% (80)	95.3% (81)			0.823
		T/T	23% (24)	4.7% (4)			
		C/C-T/T	58.7% (61)	60% (51)			0.791
		C/T	41.3% (43)	40% (34)			
		-	56% (117)	75% (128)		Allele C	
		-	44% (91)	25% (42)		Allele T	0.00014*
(Patel et al., 2017)	rs10735810	-	39.86% (55)	30.55% (22)		FF	-
		-	49.27% (68)	40.28% (29)		Ff	0.849
		-	10.87% (15)	29.17% (21)		ff	0.002*
			64.49% (178)	50.69% (73)	Indian	Allele F	
			35.51% (98)	49.31% (71)		Allele f	0.006*
(Krpina et al., 2020)	rs2228570	C/C	34.7% (41)	30.2% (36)		-	0.540
		C/T	50% (59)	57.1% (68)		-	0.347
		T/T	15.2% (18)	12.6% (15)		-	0.900
		-	59.7% (141)	58.8% (140)	European	Allele C	0.912
		-	40.3% (95)	41.2% (98)		Allele T	0.838

(Rosenfeld et al., 2017)	chr12:48272895	-	44.6%	46.3%	Jewish	FF	
		-	10.7%	12.2%		ff	0.958
		-	44.6%	41.5%		Ff	

P value <0.05 is statistically significant and they are represented by * at the top, - represents the data is not mentioned.

In table 1, the first dataset comes from (Manzon et al., 2014a), and in this research there were 98 participants. The participants were Arabs together with Jewish people. Here, among the mother's who had premature birth 62.5% have polymorphism at C>T nucleotide while only 29.2% of full-term mothers have this polymorphic change. This brings the *p* value of 0.0101 and it can be mentioned that, there is a significant difference of this polymorphic change of FokI gene between preterm birth and full-term birth mothers. According to this study, FokI gene can be a risk factor for preterm births.

The second dataset is of Brazilian ethnicity and here three distinct subtypes are present. In this research, mothers who previously gave birth to premature babies are also present. In the middle of them, between controlled group and studied group no significant difference had observed; *p* value is > 0.05 for C/C, C/T-T/T, C/C-C/T, T/T, C/C-T/T, C/T nucleotide states. It states that, though binary logistic expression, VDR gene polymorphism has no impact on reoccurring preterm birth. This study also includes the information of multiparous mothers. Amidst them, there is no significant association of the polymorphic states of FokI gene. However, the allelic states have impact on preterm birth. Allele T has a *p* value of 0.00013 making it a susceptible factor contributing to spontaneous preterm birth (Javorski et al., 2018).

The later study is on Indian ethnicity (Patel et al., 2017). This study is dedicated in finding the association amidst F allele which is wild type and f allele. The mentioned polymorphic states

are: FF, ff, Ff and allele F as well as allele f. The finding were, in 15 preterm births and 21 full-term births the ff genotype frequency was at higher point with in preterm births mothers, the stating *P* value is 0.002; again, for the presence of f allele compared to wild type F allele was noticeably higher. The *P* value of 0.006 makes f allele of FokI gene a causative factor for premature births.

(Krpina et al., 2020) examined the association of VDR SNPs in the European region among the mothers of preterm infants. This studied focused on C/C, C/T, T/T genotypes and allelic forms T and C. The estimated *P* value was higher than 0.05 in every case. From this, we can have the insight that there is no association between the FokI gene SNPs of VDR (of mother's) with preterm births.

At the bottom of the table, we can see the study of (Rosenfeld et al., 2017) which was conducted on Jewish ethnicity. This study shows no association between premature birth and mother's VDR FokI gene SNP.

3.3 Genetic Association in terms of FokI gene with Low Birth Weight

Birth in a healthy condition is crucial for disease and risk-free quality of life. One of the biggest complications of births is low-birth weight which results in many serious health issues in later life such as lower intelligence quotient (IQ), cardiovascular dysfunctions, kidney problems, and insulin resistance (Branda et al., 2022, 2023; Hovi et al., 2016; Rimol et al., 2023). Before any significant weight loss, the first measured weight of the infant within 60 minutes of birth, if is less than 2500 grams it is called low-birth weight, infant weight less than 1500 grams is said to be very low-birth weight, and finally, if the weight is <1000 grams it is called extremely low-birth weight (Cutland et al., 2017). A study conducted in India among 147,762 showed that 15.8% of infants were of LBW and 1.2% were of very-low-birth weight (Jeemon et al., 2022). This is the terrific scene in a third-world country. But in the USA alone the trait of LBW

rose by 3% from the year 2020 to 2021. Among 3,664,292 reported births, 1.38% of babies were of very- low-birth weight whereas 8.52% were of LBW (Martin et al., 2021).

The scarcity of LBW indiscriminately touches all the countries of the world, making it a major health concern. Researchers have found out the association of LBW with many factors like maternal hemoglobin level, intake of folic acid supplement, consumption of larger amount of meal during pregnancy, maternal age (Alebel et al., 2019; Desta et al., 2020; Tadesse et al., 2022). There are recent updates regarding genetic association with LBW and this study reflects on FokI gene's polymorphic change in mother's VDR with low-birth weight (Tiwari et al., 2022). This review paper will concentrate on two research articles conducted in Northeast India and European region.

Table 3: Association of birthweight with mother's VDR's SNT polymorphism.

Reference	Gene	Genotype	Infant birthweight (kg)	Ethnicity	*P*-value
(Tiwari et al., 2022)	rs2228570	Wild type genotype vs variant genotype	ff	1.56 ± 0.73	Indian	0.098
			Ff + FF	1.99 ± 0.63		
		Other types against homozygous	ff + Ff	1.98 ± 0.70		0.508
			FF	1.98 ± 0.46		

Birth weight difference between preterm and full-term birth on the basis of the presence of same SNP in the VDR of mother.

P-value <0.05 is statistically significant. SNP= Single Nucleotide Polymorphism, VDR=Vitamin D receptor.

In the table, we can see two different data sets. These data sets come from different ethnicities, one from India (Tiwari et al., 2022) and another from Europe (Krpina et al., 2020).

The data was obtained from the FokI gene's polymorphism in preterm and full-term births. There is a side-to-side observation among the presence of wild type genotype vs variant genotype as well as other genotypes against homogenous genotype. The observed nucleotide sequence was T>G. Here, the birthweights are following 1.56 ± 0.73 and 1.99 ± 0.63 for wild type genotype vs variant genotype. The statistical equation showed no significant effect of these genotypes on the birthweight as the *p*-value was 0.098. On the other hand, by plotting other genotypes against a homogenous genotype there was very little difference according to the *p*-value of 0.58 (Tiwari et al., 2022).

Again, there is another study that cross-talks between the mother's VDR SNP of FokI gene and birthweight. The study was based on the Israelian population. The analysis was executed over 187 mothers. Here, Hardy-Weinberg Equilibrium was used. As the A type allele was increasing in the mother's FokI gene due to the presence of polymorphism, the birthweight was decreasing, *p*-value was 0.04. The Chi-squared test noted *p*-value <0.05 shows an association. This results in the conclusion that FokI gene polymorphism of the mother in the VDR is responsible for lowering the birthweight.

Apart from these studies, there is very less information between the mother's VDR SNP and the birthweight of the infant. But there are significant studies that look into the matter of preterm and LBW based on genetic changes.

Chapter 5

Conclusion

In this review paper, we saw five research data for PTB and one for LBW. Here, three of the studies conducted on Jewish and Arabs, Indian, and Brazilian ethnicity showed an association between FokI gene and PTB (Javorski et al., 2018; Manzon et al., 2014b; Patel et al., 2017). Whereas, the other two studies on European and Jewish populations showed no association (Krpina et al., 2020; Rosenfeld et al., 2017). This can be said that based on these five researches PTB is associated with PTB due to the mothers' VDR SNP. On the other hand, LBW has very little information. This study states that there is a very minimalistic association of homozygous genotypes against others for LBW. However, this study failed to prove and strong association between LBW with mothers' VDR SNP.

4.1 Limitation of the study

To understand the exact correlation more research, have to be conducted on larger populations. In this study, we have also evidenced that PTB is associated with vitamin D deficiency in the mother, and vitamin D deficiency is associated with VDR SNP (Divanoglou et al., 2021). Research have be established based on associating these three factors together: VDR SNP, vitamin D deficiency, and PTB. Again, for the LBW there are very less study focused on FokI genes' SNP. Therefore, there are limited data so exactly describe the correlation.

4.2 Future Research Plan

Preterm birth and LBW are very concerning outcomes of pregnancy. As mentioned in this paper, we noticed genetic pre-deposing factor such as VDR SNP of mothers' being associated with these two factors. However, for both of the studies, the examined populations were a

particular ethnicity. This study needs to be conducted on larger population and addressing both the factors: PTB and LBW.

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