A Review on Relationship of SNP at rs2228570 of VDR Gene and Different Diseases in Different Populations.

By

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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing my 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 that has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

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Ethics Statement

This study did not involve any human participants, human specimens or tissue, vertebrate animals or cephalopods, vertebrate embryos or tissues and field research.

Abstract

Multiple disorders are caused by mutations in the vitamin D receptor (VDR) gene. The VDR gene directs the body to manufacture vitamin D receptor protein (VDR). This vitamin D receptor is engaged in vitamin D-mediated reactions. This vitamin D level is one of the most important prognostic markers for several disorders. It is believed that several disorders are related to VDR gene polymorphism. Scientists are also interested in leprosy, osteoporosis, osteoarthritis, parkinson, breast cancer, and diabetes in an effort to better understand the impact of variation in the VDR gene in disease development in different populations. Additionally, many studies have associated vitamin D with enhanced immunological function. Consequently, this polymorphism may contribute to the emergence of the above-mentioned disorders. This study proposed that a particular nucleotide polymorphism (SNP) at rs 2228570 site of the VDR gene is associated with different diseases.

Keywords: Rheumatoid Arthritis, Parkinson's Disease, osteoporosis, Single nucleotide polymorphism, VDR gene, and Vitamin D receptor.

Dedication

This thesis project is dedicated to my beloved parents.

Acknowledgement

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List of Acronyms

RA	Rheumatoid Arthritis
VDR	Vitamin D Receptor
SNP	Single Nucleotide Polymorphism
RS	Restriction Site
DBD	DNA binding domain
LBD	Ligand binding Domain
CKD	Chronic kidney disease
AKD	Acute Kidney Disease
CVD	Cardio vascular disease
HLA	Human Leukocyte Antigens
BMD	Bone Mineral Density
PMOP	Post-menopausal osteoporosis
NAN	Non-American Native
OP	Osteoporosis
PD	Parkinson's Disease
DMARDs	Disease-modifying anti-rheumatic medicines

Chapter 1

Introduction

1.1 Background

The Vitamin D Receptor (VDR) gene encodes a protein essential for keeping strong bones and teeth as well as regulating the immune system. This gene encodes the protein VDR receptor. The Vitamin D Receptor (VDR) is a protein located on the cell surface of numerous tissues in the body, including the bones, skin, and immune system. Unfortunately, the VDR polymorphism can result in several diseases. Polymorphisms can have numerous consequences on the function of the gene and the protein it encodes. These polymorphisms can have diverse consequences on the gene's function and the protein it encodes. Rheumatoid arthritis, breast cancer, Parkinson's disease, and osteoporosis are the disorders related with VDR polymorphism. In my pursuit of knowledge on the cause and management of this illness, It was discovered that vitamin D has potent anti-inflammatory properties. Additionally, vitamin D has the potential to be a powerful regulator of calcium homeostasis, aiding in the immunomodulatory impact. Therefore, it was crucial to comprehend how vitamin D was controlled by the body. That is why this review aims to find the connection between vitamin D and different diseases and the single nucleotide polymorphism at the FokI site of VDR gene. Here, the VDR polymorphism is studied at both allelic and genotypic levels to understand this association for a better understanding for this review purpose

1.2 Vitamin D receptor

It was found that the VDR is a steroid hormone receptor, which is a member of the superfamily of steroid hormone receptors, and displays ligand-dependent gene regulation (Mohammed et

al., 2021a). The protein that is known as the vitamin D receptor is responsible for facilitating the biological effect of vitamin D. Researchers have discovered that the vitamin D receptor is an essential component of an immune response because it directs the mechanisms that occur post-transcriptionally. This discovery was made in an effort to comprehend how the receptor works (Singh et al., 2018). With the assistance of VDR, the immune system can be stimulated in this manner as response to vitamin D. The VDR gene is responsible for the production of the VDR protein, which assists vitamin D in forming a binding complex with its receptor and in carrying out its function. Researchers have already discovered that the immunomodulatory effect that has on diverse populations can be attributed to vitamin D. For example, the relationship of rs2228570 in the population of Canada has a variant in the gene that encodes for the vitamin D receptor (HITCHON et al., 2012). Because of this, a polymorphism in the binding site of vitamin D, known as VDR, has been linked to the autoimmune illness RA, a chronic inflammatory condition. The expression of the VDR gene can be connected to one's ethnicity, which in turn can have an effect on the genetic relationship in a different populations (Mohammed et al., 2021a). Different populations have their own unique patterns of gene expression as a result of this factor. VDRs are regarded to be indispensable for vitamin D due to the fact that vitamin D cannot carry out its activities without these (Medeiros et al., 2020). According to the findings of the study, it has been discovered that VDR interacts with 1,25(OH)2D3 in the nucleus of human cells, which causes genomic expression to be produced (Medeiros et al., 2020).

1.3 VDR gene

The gene that encodes the Vitamin D3 receptor is the VDR gene. The VDR gene is considered a nuclear hormone receptor family member. This gene codes a specific protein. The function is to commands to make a protein which is VDR. This receptor VDR is essential as our body

reacts to vitamin D through this. Mutation of this gene is the reason behind different diseases. For example, different autosome recessive diseases can be associated with an increasing level of vitamin D following the mutation has occurred. DNA binding and ligand binding domain for vitamin D are present in this receptor (Tseng et al., 2017). The DNA binding domain (DBD) is a hydrophilic domain while the ligand binding Domain (LBD) is hydrophilic (Nguyen et al., 2002). In the DNA or Ligand binding different mutation takes place thus showing different distinct and variable phenotypes (Tseng et al., 2017). As an example, a missense mutation of tryptophan founded on the ligand binding domain (LBD) of VDR is found to show resistance characteristics to 1,25-dihydroxy vitamin D (Nguyen et al., 2002).

1.4 Importance of vitamin D

One of the vitamins that are soluble in fat is calciferol, often known as vitamin D. This vitamin may be obtained in a wide variety of various dietary supplements as well as natural foods. There are two distinct types of vitamin D, these are vitamin D3 and vitamin D2 (Lips, 2006). The skin is capable of producing the active form of vitamin D3 when exposed to sunshine under the appropriate conditions (Lips, 2006; H. Zhang et al., 2022). In order for them to enter the cells, the liver and the kidney must first hydrolyze them so that they may be converted into their active form (Holick, 2003). Throughout an individual's whole life, the presence of this crucial component is very needed for the formation and expansion of bones that are healthy (Holick, 2003). The active form of this vitamin is beneficial because it increases the amount of calcium that is absorbed from the digestive system (Lips, 2006). The metabolically active form of vitamin D exerts its substantial influence by promoting the movement of calcium into the circulatory system from the various organs in the body (Lips, 2006). Because of this, vitamin D is able to perform one of its most important roles, which is to maintain the homeostasis of calcium. This is accomplished by increasing the amount of calcium that is absorbed from the

gut (Holick, 2003). Vitamin D is very necessary for normal bone development and bone remodeling to take place. In addition, vitamin D has a role in the immunological system. The VDR receptor is capable of accepting the active form of vitamin D. Due to the presence of the VDR receptor on activated T and B cells, it is able to both prevent the cells from engaging in excessive cell division and stimulate their expansion beyond their normal limits (Holick, 2003). This is one of the ways in which vitamin D can support the function of the immune system. Rickets was the first disease that could be clinically described as being caused by a lack of vitamin D, and it was first identified in the 20th century (Lips, 2006). According to a number of studies, rickets was seen most frequently in children; however, older individuals now have a greater risk of developing a condition caused by a D3 shortage. Next, as a consequence of low blood calcium and vitamin D levels, bone turnover and bone resorption may take place as the probability of PTH secretion rises. This is due to the fact that the likelihood of PTH production is increased (Lips, 2006). A lack of vitamin D3 has been found to be associated not only with acute kidney disease (AKD), but also with chronic kidney disease (CKD) in more recent times (H. Zhang et al., 2022). In conclusion, it raises the blood calcium level while simultaneously lowering the PTH level, both of which are essential for ensuring that the bone density remains at a healthy level and for contributing significantly to the immune system's capacity to combat cancer. Additionally, vitamin D plays a significant part in ensuring normal bone density is maintained.

1.5 Single Nucleotide Polymorphism in VDR gene

Single nucleotide polymorphisms are a type of genetic variation that occurs when there is a change in the sequence of only one nucleotide inside the DNA. These nucleotides include adenine, guanine, thymine, and cytosine (SNPs). Because of this change in the VDR gene, a variety of disorders have been discovered that are connected to this polymorphism.

Polymorphisms in the VDR gene have been linked to a number of disorders, including rheumatoid arthritis (Punceviciene et al., 2021). The VDR gene is incredibly important to the process of absorbing vitamin D in the body. This vitamin D attaches to the receptor, which then allows it to have the impact we want it to (Mukhtar et al., 2019). These single nucleotide polymorphisms in the VDR gene have an effect on how the body reacts to supplemental vitamin D, which is why these SNPs are connected with a variety of disorders. Such conditions include osteoporosis, autoimmune illnesses, cancer, and cardiovascular disease. A variant of the VDR gene called FokI, which is known as a single nucleotide polymorphism (SNP), has been discovered to be related to leprosy (Singh et al., 2018). As was indicated before, the primary polymorphism sites that demonstrate a relationship with a variety of disorders are found in multiple VDR genes. These VDR gene polymorphism site include FokI, BsmI, ApaI, and TaqI (Yadav et al., 2020). A direct link between the FokI gene and an increased risk of developing rheumatoid arthritis and multiple sclerosis has been discovered by others (Tizaoui & Hamzaoui, 2015a). Numerous pieces of study have pointed to the possibility that this SNP may potentially influence the immunological response of the body (Singh et al., 2018).

1.6 Disease associated with VDR gene polymorphism

1.6.1 Rheumatoid Arthritis

In general, rheumatoid arthritis, often known as RA, is one of the autoimmune diseases. In this condition, the body's healthy cells are targeted for destruction by the immune system, leading to inflammation in various places of the body and varying degrees of discomfort. In addition to this, those who have rheumatoid arthritis have pain in their joints, stiffness, swelling, soreness, and fever (Smolen et al., 2016). Other clinical signs of rheumatoid arthritis include palpitation, soreness, and thickening of the synovial membrane. Rheumatoid arthritis is characterized by certain articular characteristics (Lee & Weinblatt, 2001). Although the exact

causes of rheumatoid arthritis (RA) have not been identified, research has shown that environmental factors and genetic predispositions have a role in the disease's development (Jiang & Alfredsson, 2020). Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune illness, and other research have supported the hypothesis that some hereditary variables as well as environmental factors may play a role in its development (Giannini et al., 2020). Additionally, rheumatoid arthritis (RA) is recognized as a systemic inflammatory illness that causes systemic damage to the joints and leads to bone (Tizaoui & Hamzaoui, 2015a). Many researches have also determined that around one percent of the population is afflicted by RA, and that the probability of developing this disease can occur at any age; however, it is most typically seen in persons in their forties and their seventies (Lee & Weinblatt, 2001). The proximal interphalangeal (PIP) and metacarpophalangeal (MCP) joints of the hand and foot are typically the first to be impacted by this condition. Further research has led to the realization that unfavorable prognostic variables are partly to blame for the deterioration of the muscles and joints (Lee & Weinblatt, 2001).

1.6.2 Leprosy:

Variations in the VDR gene can affect a person's capacity to fight off illnesses like leprosy since the VDR gene is essential for controlling the immune system (Paz et al., 2021). The VDR gene is a member of the HLA gene and genetic studies have found that these genes are responsible for developing infectious diseases like leprosy (Neela et al., 2015; Singh et al., 2018). The results of several investigations looking into the connection between VDR polymorphisms and leprosy susceptibility have been conflicting and frequently contradictory. While other studies have shown no conclusive link, others have hypothesized that certain VDR polymorphisms may raise the likelihood of acquiring leprosy as no studies can explain the haplotype association of leprosy (Neela et al., 2015). Although the cause of these contradictory

results is not yet known, it might be because of variations in research design, demographics, or other elements. For instance, a study in India has shown no association of TaqI polymorphism in developing leprosy but is found to be associated with the Mexican population (Neela et al., 2015). That's why further study is required to understand the association between VDR polymorphisms and the illness.

1.6.3 Osteoporosis:

By directing the activation of genes involved in bone production and resorption, the Vitamin D Receptor (VDR) gene plays a critical part in regulating bone metabolism (Holick, 2003). Changes in the Vitamin D Receptor's expression or function may result from polymorphisms, or variants, in the VDR gene. Bone mineral density (BMD) is considered to be a crucial determinant of bone strength (Choi et al., 2000). Studies have revealed a link between certain VDR gene polymorphism and BMD in elevating osteoporosis (OP), a disorder marked by decreased bone density and an elevated risk of fractures (Choi et al., 2000; Gu et al., 2009). VDR gene polymorphisms and osteoporosis, however, have a complicated association that may be impacted by a variety of other variables, including age, sex, lifestyle, and environmental factors. Along with VDR different other genes can also have an influence as a factor for osteoporosis (Gu et al., 2009). For instance, high vitamin D intake, which is crucial for good bone health, may mitigate the impact of VDR gene polymorphisms on the risk of osteoporosis (Holick, 2003; Lips, 2006). It's also crucial to remember that VDR gene polymorphisms are only one of several things that contribute to the onset of osteoporosis. In recent years, studies have found that the association between FokI and BMD is responsible for bone weakening in Korean, and Asian postmenopausal women (Choi et al., 2000). In contrast, no significance in the Caucasian population. Along with this VDR polymorphism also shows the indication of women having post-menopausal osteoporosis (PMOP) (L. Zhang et al., 2018). In conclusion,

despite the fact that VDR gene polymorphisms can raise the risk of osteoporosis, they should just be one of many variables taken into account when assessing a person's overall bone health. Effective prevention and management of osteoporosis need a comprehensive strategy that takes into account both hereditary and environmental variables risk.

1.6.4 Parkinson

Low vitamin D levels in Parkinson's disease (PD) patients were first identified in 1997 (Evatt, 2014). Movement and coordination are affected by the neurodegenerative condition Parkinson's disease (Evatt, 2014). It is caused by the loss of dopamine-producing neurons in the brain, resulting in symptoms such as tremors, stiffness, sluggish movements, and balance and coordination difficulties (Agarwal et al., 2020). The specific etiology of Parkinson's disease is unknown, but genetic and environmental factors are believed to have a role (Agliardi et al., 2021). The condition normally develops gradually over time. There is presently no cure for Parkinson's disease, however, treatments such as vitamin D as supplement medication and physical therapy can help control symptoms (Evatt, 2014). In rare instances, surgery may be a viable alternative. Individuals with Parkinson's disease must collaborate closely with their healthcare team to build a thorough treatment plan that matches their specific requirements. Parkinson's disease can have a substantial influence on everyday living, but persons with the condition can continue to live active and rewarding lives with the proper assistance (Agarwal et al., 2020; Agliardi et al., 2021).

1.6.5 Breast cancer

Malignant cells, also known as cancer cells, can occur in the breast tissue of a person who has the condition known as breast cancer. It is the type of cancer that occurs in women more frequently than any other type, and while men can get it too, it is a far less prevalent form of

cancer in males (Dean et al., 2011). Age, gender (being a woman), a family history of breast cancer, certain genetic mutations (such as BRCA1 and BRCA2), exposure to estrogen, alcohol consumption, obesity, and a personal history of breast conditions such as benign breast lumps are all risk factors for developing breast cancer (Buyru et al., 2003). Other risk factors include a personal history of breast conditions such as benign breast lumps. In certain research, a particular VDR polymorphism was shown to be related with a lower risk of breast cancer (Buyru et al., 2003). However, in other investigations, this association was not found to be present. This disparity may be attributable to variances in the research populations, such as variations in ethnicity, lifestyle variables, and other breast cancer risk factors (Lue & Crew, 2015).

1.7 Objective

This review article on single nucleotide polymorphism of the FokI gene and its relationship with rheumatoid arthritis and its association with different diseases seeks to provide readers a descriptive insight into the state of knowledge in these areas. This article will focus on the most current scientific breakthroughs in the quest to understand the underlying mechanisms that contribute to RA, OA. OP, PD and Breast cancer as well as the diagnostic criteria and techniques that are used to detect the condition and the various patient treatment options. This review will also explore the limitations and challenges faced by medical practitioners while treating these diseases, and it will point out areas in which further research is necessary. The primary goals of this review are to provide researchers, clinicians, and patients with an up-to-date and comprehensive overview of mentioned disease associated with VDR FokI polymorphism as well as to highlight the significance of ongoing research in terms of improving our understanding of and capacity to treat this debilitating disease.

Purpose: The purpose of this study was to determine the association of VDR gene polymorphism in different population. Along with this to explore the effect of the polymorphism in VDR gene in those patients.

Significance: These concepts are useful in understanding the etiology and the relation of VDR polymorphism in developing mutative disorders.

Chapter 2

Materials and Methods

For the purpose of this review, I chose 40 different articles as samples pertinent to this subject since I believe that doing so would better enable me to comprehend the primary focus of the article. The databases of reputable sources, such as PubMed, Google Scholar, Springer, Nature, and Science Direct, were thoroughly searched in order to locate all of these papers. In order to guarantee the credibility of the information that will be incorporated into my review investigation, I felt it necessary to incorporate articles from the aforementioned websites. To search the articles, I used the keywords VDR, rheumatoid arthritis, polymorphism, breast cancer, Parkinson, and SNP to get related desired articles. After gathering all of the necessary data for the study, I set out to investigate the relationship between a single nucleotide variation in the VDR gene and the beginning of rheumatoid arthritis. In this article, APA 7th citation is used and proper acknowledgment is given to the authors. Through reading these studies, I was able to increase my knowledge of the VDR gene mechanism as well as the beginnings of rheumatoid arthritis. My review led me to uncover that a single nucleotide polymorphism in the VDR gene's site FokI that is the root cause of the illness known as rheumatoid arthritis, osteoporosis, breast cancer, and Parkinson's. In patients with rheumatoid arthritis, genotyping investigations and the distribution of alleles are discussed in a number of published articles. These findings lent credence to my hypothesis that the majority of individuals who have VDR polymorphism also suffered from different diseases. This review was completely created based on the material collected from a number of different sources; at no time did any subjective opinions or assessments come into play.

Chapter 3

Result & Discussion

3.1 Result

A study was done in central India to understand the relationship between VDR polymorphism in FokI (rs10735810) and rheumatoid arthritis. The number of patients that were kept in the case study group was one hundred and twelve and about one hundred twenty-five patients were kept in the control group. They developed an overall genotype pattern and declared that VDR polymorphism has no significant association with RA susceptibility (Shukla et al., 2014). According to the study, the 'FF' genotype showed an increase in number to the control group (51.7% versus 43.2%) and in contrast, the genotype 'ff' showed higher compared to the case group (Shukla et al., 2014). The allele distribution that the is found in the Indian population is not that significant but the F allele frequency was higher in the case group and the f allele in a controlled group (Shukla et al., 2014). Additionally, there was no discernible difference in the carriage rate of those alleles between the RA group and the healthy control group. So, according to these finding the suggested no association of VDR FokI (rs10735810) polymorphism in rheumatoid arthritis susceptibility (Shukla et al., 2014).

Another study was conducted in the Pakistani community to determine whether cousin marriage is the primary cause of passing the genetic disease, as cousin marriages account for roughly 70% of marriages in that country (Mukhtar et al., 2019). They tried to invent the relation in between rheumatoid arthritis and VDR gene polymorphism. According to their study, exon 2, allele "C," which acts as the toxic allele for the beginning of rheumatoid arthritis, is present at the polymorphic position rs10735810 of the FokI gene (Mukhtar et al., 2019). Here, in the single site analysis the coefficient interval and the odd ratio were calculated at

about 0.82~2.44 and 1.42 in rheumatoid arthritis (Mukhtar et al., 2019) On the other hand, the outcome of the genetic test for the genetic variation reveals that the case group's frequency of "CC" and "CT" was observed to be more frequent than the controlled group at the FokI (rs10735810) site (Mukhtar et al., 2019). A genetic analysis conducted on a Brazilian population demonstrates the link between VDR and rheumatoid arthritis (Cavalcanti et al., 2016). Additionally, the regression analysis model discovered that this SNP was linked to the development of RA. Haplotype analysis was used to support their claim that the TTGT haplotype is more likely to be protective against the disease than the CGAT, CGGA, CGGT, CTAA, CTAT, TGAA, TGAT, TGGA, and TTGA haplotypes, which were all claimed to be related with the disease's start (Mukhtar et al., 2019). Also, by assessing through the Hardly-Weinberg equilibrium all genotyped frequencies were assessed in the Brazilian population to suggest some strong linkage between the SNP polymorphism and RA (Cavalcanti et al., 2016). Therefore, thus can be concluded that there was a correlation between the VDR FokI polymorphism and susceptibility to rheumatoid arthritis (Mukhtar et al., 2019; Tizaoui & Hamzaoui, 2015b).

Another study conducted on the French population found a difference between the transmission and non-transmission of F and f alleles, with a p-value of 0.01 indicating a significant difference (Maalej et al., 2005). The transmission rate of the parents' F allele was much higher, at 62.88% (Maalej et al., 2005). The FF genotype was discovered to be more prevalent in RA patients than in the control group during the genotyping study (Maalej et al., 2005). Additionally, the FF genotype was shown to be more prevalent among the 45 RA patients in comparison to the control group (Maalej et al., 2005; Tizaoui & Hamzaoui, 2015b). Based on the findings of their investigation, the F allele was examined to see whether FokI had a connection with rheumatoid arthritis. This analysis is done to the patients where the patient carried at least one HLA-DRB1 SE allele (Maalej et al., 2005) The results demonstrate that the

F allele was passed forward, as well as the existence of RA in the first-degree relative (Bagheri-Hosseinabadi et al., 2020; Maalej et al., 2005). In another study that was conducted on the Egyptian population also matches these findings. According to their study, there was also a higher percentage of both f allele frequency and FF genotype wasfound in the case group which was 72% and 54.5% (Mohammed et al., 2021b). They added that the case study group had the genotype for the VDR FokI polymorphism (T>C) (Maalej et al., 2005).

The study that was done native North American population backed up the theory that VDR polymorphism is linked to rheumatoid arthritis (HITCHON et al., 2012). The single nucleotide polymorphism of FokI was found to be related to RA in their study. This association was discovered using both and dominant models in control group (HITCHON et al., 2012). In RA patients, the allele frequency of F/C was 0.44 (HITCHON et al., 2012). They thus asserted that polymorphisms in the vitamin D receptor may be responsible for the greater prevalence of RA in NAN populations (HITCHON et al., 2012).

The relationship between this condition and the amount of vitamin D has been the subject of research that was done on the Lithuanian population (Puncevičienė et al., 2021). They selected RA patients who were taking vitamin D supplements as well as those using disease-modifying anti-rheumatic medicines (DMARDs) for this study (Puncevičienė et al., 2021). The results demonstrate that 61.55% of RA patients (n=127) had insufficient levels of vitamin D, which was dramatically lower than that of the healthy control group (50 nmol/L) (Puncevičienė et al., 2021).

This study aims to provide proof that a vitamin D deficiency may contribute to RA. This finding was contrary to (Mukhtar et al., 2019) who found the vitamin D level to be sufficient in Pakistani RA patients. The data supports their claim by demonstrating that patients using vitamin D supplements had reduced RA DAS28 CRP scores (Bugaj et al., 2022; Puncevičienė

et al., 2021). This data implies that reduced disease activity is linked to greater vitamin D concentrations. Another study that was done on the Egyptian population also finds a lower vitamin D level in RA patients (Mohammed et al., 2021b). In contrast, they do not discover any relationship between the VDR gene Foki since there was no discernible difference between the case study group and the control group ($p>0.05$) (Punceviciene et al., 2021). The study in the Lithuanian population did not show a link between VDR and RA, but it did show that vitamin D insufficiency was common (Punceviciene et al., 2021).

Aside from this, there is no connection of FokI found among the breast cancer patients in the Chinese community (Cui et al., 2001). According to the results of their haplotype analysis, Bsm and TaqI have been shown to have a connection to breast cancer (Cui et al., 2001). This is because the study reveals a distribution of the t-allele and the A-allele. The researchers came to the conclusion that the tA haplotype is related with an increased risk of breast cancer in the Chinese population (Cui et al., 2001). In contrast to what was shown in the Chinese population, research conducted by (Kazemi et al., 2022) on Iranian populations found a connection between the FokI(rs2228570) polymorphism and an increased risk of breast cancer. They stated that the frequency of the FokI haplotype was greater than that of other haplotypes (Kazemi et al., 2022).

Parkinson's disease (PD) is yet another alarming condition that has been connected to VDR (Agliardi et al., 2021). According to the findings of a study, the allele distribution of the control group and the case study group of the Italian population was shown to be significantly different from one another (Agliardi et al., 2021).In addition, 33.5% of people have the "CC" gene, which is thought to be a protective genotype in PD (Agliardi et al., 2021). In addition to this, it has been demonstrated beyond a reasonable doubt that the VDR FokI C variation is superior to the FokI T variant in terms of its performance as a transcription factor (Agliardi et al., 2021).

3.2 Discussion

The VDR gene polymorphism and its relationship to different diseases are being investigated in several populations in this study. VDR Foki gene polymorphism has been discovered to be associated with different disease development such as arthritis, breast cancer, and leprosy in many ethnicities. On the other hand, the VDR gene polymorphism was not identified in certain populations. For instance, no significant correlation between this type of SNP was found among Indian populations for RA (Shukla et al., 2014). No, a meaningful result was not discovered in either the phenotypic or allelic analyses. It was established that the case study group contained individuals with the FF genotype. This indicates that, as compared to the case study group, RA patients had a larger percentage of the FF genotype (Shukla et al., 2014). Additionally, in the control group of the Indian population, the F allele frequency was much greater. These findings in the Indian population led to the conclusion that VDR polymorphism and RA were unrelated. In contrast, a significant correlation between the VDR FokI gene and rheumatoid arthritis was discovered in the Brazilian population (Cavalcanti et al., 2016). However, the likelihood of passing on certain genetic illnesses was substantially higher in the Pakistani group due to the higher cousin marriage rate. They discovered many haplotypes connected to the illness. The case study group contained this haplotype. Additionally, it was shown that the TTGT haplotype was more resistant to rheumatoid arthritis (Mukhtar et al., 2019). In their genetic results, they discovered that the "CC" and "CT" were more common in the case study group of RA patients (Mukhtar et al., 2019). For the development of rheumatoid arthritis in the Pakistani community, where cousin marriage was more prevalent, this C allele is identified as the hazardous allele. These results are also supported by research in the French population, where it was concluded that the F allele is passed on from parents to children (Maalej et al., 2005). They also back up the assertion made by the Pakistani community that the French population has a higher prevalence of RA patients with the FF genotype. These results are similarly consistent with the

Egyptian population, where 54.5% of the case study group's members had the FF genotype (Mohammed et al., 2021b). Additionally, they discover the mutation in the VDR FokI gene's C and T alleles. However, different research that was conducted in the Egyptian population showed no correlation between the VDR FokI polymorphism and the onset of rheumatoid arthritis, although they did claim in their evidence that RA patients have lower levels of vitamin D (Tizaoui & Hamzaoui, 2015b). Therefore, monitoring vitamin D levels in RA patients can have a significant influence on the progression of the illness. To determine if the VDR Foki gene polymorphism was indeed the cause of RA or not, several populations have used various study designs. Therefore, it is impossible to declare a connection based on a single research. However, the majority of research has discovered a direct link between VDR polymorphism and the onset of RA.

Among the other diseases associated with VDR FokI polymorphism and breast cancer is being examined in the Iranian population where the FokI (rs2228570) revealed a higher connection ratio (Cui et al., 2001). This is one of the other diseases related with VDR. In Iranian population, the breast cancer-causing haplotype was shown to be more prevalent than in the group that served as a control (Kazemi et al., 2022). On the other hand, there was no association observed between the VDR polymorphism and breast cancer in the Chinese population. However, BsmI and TaqI were determined to have proved their role in the development of breast cancer (Cui et al., 2001). FokI was not associated with the disease in any way. According to what they found, the t and A alleles are more common, and the tA haplotype can raise the risk of breast cancer (Cui et al., 2001).

Another neurological illness that has been linked to a variant of the VDR gene called the FokI polymorphism. There is evidence from research that the VDR FokI C variation performs better as a transcription factor than the FokI T variant does (Agliardi et al., 2021). These findings lent

clearance to the hypothesis that the FokI polymorphism in VDR is connected to Parkinson's disease (Agliardi et al., 2021).

The other diseases are mostly contradicted by research on other populations. For instance, Chinese population and Italian population shows the contradictory result on the association between FokI and breast cancer. In the Chinese population, they found no association of FokI with breast cancer (Cui et al., 2001) but the Italian population has a significant association with FokI (Kazemi et al., 2022). Apart from this study for the PD, the results are also the same where the association is detected in a population but scattered results in different populations.

3.3 Treatment Aspects

The treatment for the diseases mentioned, which is caused by a variation in the VDR gene FokI, has not yet been thoroughly researched. Patients with this disease were evaluated in several of the groups, and their vitamin D levels were measured. When it comes to managing the symptoms, using vitamin D supplements can be an effective therapy option. Due to the fact that a low vitamin D level has some connection to the development of the condition (Mosaad et al., 2014). Therefore, taking the dietary supplement Vitamin D is associated with a reduced incidence of RA (Mosaad et al., 2014). According to research carried out on the Lithuanian population by (Puncevičienė et al., 2021) it was found that treating vitamin D insufficiency with vitamin D supplementation may be an option for treating RA. In addition, found that individuals with RA who were treated with vitamin D showed modest clinical improvement (Ateş, 2011). Vitamin D can be helpful in the treatment process in addition to the nonsteroidal anti-inflammatory drugs (NSAIDs) that are often used for pain relief. In addition, this can help enhance the body's control of calcium (Mohammed et al., 2021b). Vitamin D supplements are often prescribed to patients suffering from osteoporosis in Pakistan (Mukhtar et al., 2019). Another study related to breast cancer suggested that both premenopausal and postmenopausal

women who were vitamin D deficient had an increased risk of developing breast cancer (Atoum & Alzoughool, 2017).

Chapter 4

Conclusion

Vitamin D has a substantial effect on the function of the immune system. To carry out its intended tasks, vitamin D must interact with vitamin D receptors. With the help of this vitamin D receptor, the body reacts to vitamin D when it is consumed. The VDR gene is responsible for the production of a protein known as the VDR. As a result of variations in the VDR gene, the immune system might harm the joints, which can lead to pain, inflammation, and stiffness, which are all signs of rheumatoid arthritis and breast cancer. The VDR FokI gene has been implicated in the pathogenesis of diseases by a number of different research groups. A number of other organizations were not successful in establishing an appropriate relationship. On the other hand, research has shown that those who have breast cancer, RA, OP or Parkinson's disease might have lower amounts of vitamin D. Because of this, it is clear that vitamin D may play a part in the progression of such diseases. However, the specific cause is not yet fully understood. Even though the VDR gene FokI polymorphism has been connected to a variety of communities, there are still a lot of other factors that aren't fully known that might play a part in the development of these disorders in some groups. Also, the fact that these data are so dispersed demonstrates that the polymorphism on FokI changes depending on the individual's ethnic background. There is no correlation between susceptibility in one group and another people's susceptibility. Because of this, further study is necessary before it can be concluded that the relationship between VDR FokI and these diseases. It's possible that the reason is different populations and also because of differences in age, gender, and a wide range of other characteristics. These diseases have been related to the VDR gene FokI polymorphism as a consequence of this since it has been demonstrated in a number of different groups. To summarize, the VDR FokI polymorphism has been shown to have a relationship in a variety of

groups; nevertheless, further research is required to validate the hypothesis that this polymorphism is connected to different diseases in order to have a better understanding of the topic.

Future Aspects

The study of VDR polymorphism has emerged as an important element of genomics research. VDR polymorphism studies are anticipated to play a major role in personalized medicine, illness detection, and genetic testing as a result of technological developments and decreased sequencing costs. In the future, research of VDR polymorphism will enable the discovery of genetic changes linked to illnesses and the creation of targeted therapeutics. In addition, VDR polymorphism research will play a significant role in the advancement of precision medicine. By detecting genetic variants, researchers are able to build more robust and effective treatment options. Overall, investigations of VDR polymorphism will continue to be an essential component of genomic research, and their applications will only continue to increase as technological progress continues. VDR polymorphism research have the potential to transform our understanding of illness and enhance human health.

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