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The Role of Functional Polymorphic Variants in VDR and MTNR1B Genes and Their Association with The Risk of Leukemia Development

Fatema Ali Khan[1]*, Krithika Badri[1], Dr. Vasavi Mohan[1,2]

1- Vasavi Medical & Research Centre, Lakdikapul, Khairatabad, Hyderabad - 500004 Telangana State, India.
2- Department of Genetics, Apollo Diagnostics, AHLL, Balanagar, Hyderabad. India.

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ABSTRACT

Vitamin D and Melatonin partake in complex pathways in cancer signaling. Melatonin helps prevent tumor formation and progression. Similarly, Vitamin D displays immunomodulatory effects and antitumor properties. Vitamin D and Melatonin display anti-angiogenic, antiproliferative, and anti-inflammatory effects in malignant conditions. Enhanced serum levels of Vitamin D and Melatonin are associated with reduced incidences of various cancers. Receptor variants might impact the effectiveness of the anti-cancer action of these hormones in offering respite from the side effects of malignant transformation as well as the side effects of cancer treatment. Therefore, the role of these receptor variants should be well-analyzed before aiming for their use as treatment modalities.

Our study analyzed two functional polymorphic receptor variants, one for each hormone. Our study supported the role of VDR gene polymorphism rs2228570 with T-allele showing significant association with pre-leukemic aplastic refractory anemia cases as well as leukemic cases, MTNR1B gene rs10830963, G-allele was associated with the risk of leukemia development. We conclude that genotype analysis and additional routine serum analysis will bring forth the impact of these polymorphisms on disease severity and progression, and it can help explore and offer us more clarity on identifying individuals who can benefit from additional supplement-based treatments and the treatment recommended could be more precise.

Keywords - Vitamin-D Receptor, Melatonin Receptor, Leukemia, Cancer treatment.

Introduction

Vitamin D or cholecalciferol in its active form- 1,25-dihydroxy vitamin D (1, 25-$(OH)_2$ D3) is a prohormone, which has a crucial role in bone development and maintaining its structural integrity by mediating calcium and phosphate absorption and retention from the intestine and redirecting it to the bones. It partakes in calcium homeostasis, balances electrolytes, regulates blood pressure, and modulates immune response. Sunlight UV-B exposure triggers Vitamin D synthesis and is the primary source of vitamin D. Its pro-vitamin form synthesis occurs at the cutaneous level of skin upon direct exposure to the sunlight, and its concentration depends on latitude, seasonal availability of natural sunlight, use of sunscreens, and natural pigmentation in skin melanocytes. Vitamin D is fat-soluble, and dietary resources such as Lichens, mushrooms, and ergocalciferol in plants can provide a natural source of Vitamin D. Direct exposure to sunlight leads to the synthesis of Vitamin D in the form of cholecalciferol.

Vitamin D mediates its action via its receptor, Vitamin D receptor or VDR, a nuclear transcription factor from the steroid hormone receptor superfamily. Vitamin D action primarily controls transcriptional activation of VDR by binding to its ligand binding domain (LBD). Upon interaction with its ligand, Vitamin 1α,25$(OH)_2$D3, VDR forms an activation mediated complex. Post-activation VDR acts as a transcription factor and drives forward downstream signaling involved in regulating genes involved in calcium/phosphate homeostasis, cellular proliferation, and cellular differentiation, and it also helps generate immune responses. VDR is expressed on most nucleated cells in variable concentrations and has a broad range of actions. Vitamin D displays potent genomic regulatory action and curtails cancer progression. Studies have linked newly diagnosed cases of certain leukemia types with reduced levels of Vitamin D and display a significant association with poor disease outcomes. Vitamin D action primarily controls transcriptional activation of VDR by binding to its ligand binding domain. Cells express VDR when they require Vitamin D to potentiate its action in the cytoplasm and the nucleus. VDR forms a complex with the retinoid X receptor (RXR) and is crucial for activating its functional form as a transcription factor. Studies suggest that the heterodimerization of the RXR-VDR complex leads to its transport from the cytoplasm to the nucleus, wherein this complex interacts with vitamin D response elements (VDRE) in DNA to initiate gene transcription [1, 2, 3, 4, 5 & 6].

The FokI rs2228570 polymorphism is generated due to a T to C nucleotide change in exon-2 within the first ATG start codon. This site contains a FokI restriction endonuclease site (f -allele/ T-nucleotide) where the absence of the restriction site (F-allele/ C-nucleotide) results in an alternate but less efficient start codon ACG. The outcome of this variation is that the f-allele/T-allele generates a three amino acid long extended version of the protein due to an alternate ATG start codon and reduced activity compared to the shorter VDR of the F-allele/C-allele. An in-vitro study has demonstrated that the short F-VDR versus long f-VDR protein levels correspond with variation in transcriptional activity. Enhanced VDR protein expression interplay with immune transcription factors declines its transcriptional activity. Fok-I polymorphism drives immune signals via NF-κB transcriptional activity, with shorter F-VDR having a more pronounced functional impact when compared to long f-VDR. In vitro FokI genotypes have been linked to variable interaction with different transcription factors involved in immune signaling. The FokI polymorphism alters the immune cell proliferation and cytokine signaling, consequently impacting the immune response. FokI genetic variant genotype of VDR in individuals with vitamin D deficiency could have a combined effect on immune deregulation. The VDR protein displays reduced action in response to Vitamin-1,25(OH)2D3 stimulation and has an altered cellular response. Additionally, reduced circulating levels of 25(OH)D combined with Fok-I polymorphism have been associated with the risk of various conditions, which include metabolic diseases, hypertension, autoimmunity, diabetes, poor sleep quality, anemia, and the risk of developing cancers [7, 8, 9,10, 11, 12 & 13].

Methoxyindole melatonin (N-acetyl-5-methoxytryptamine Melatonin) synthesis primarily occurs in the pineal gland, followed by synthesis in lymphocytes, bone marrow, and thymus. Melatonin participates in adaptive and innate immune modulation primarily via its interaction with high-affinity membrane receptors and secondly via nuclear binding sites available in circulating lymphocytes, spleen cells, and thymocytes. Melatonin is a chronobiotic hormone that has different phases of synthesis that follow a circadian fashion and contribute to its ability to regulate sleep, immune functions, and glucose homeostasis. It also functions as a potent ROS scavenger, balances oxidative stress via antioxidant generation, and contributes to anti-inflammatory action. Melatonin exists across diverse organisms and species, which includes all prokaryotes, eukaryotes, and higher eukaryotes. In vertebrates, melatonin synthesis depends on the duration of light exposure, followed by subsequent synthesis in the dark phase. In humans, two melatonin receptors, the MT-1 and the MT-2 are found in various tissues and organs and bound to G-proteins coupled receptors, particularly the Gα i/o GPCR, and control the intracellular cyclic-AMP levels upon ligand-mediated activation. Melatonin can also activate apoptosis in leukemic cells by regulating the levels of ROS generated. Additionally, melatonin can decrease the expression of h-TERT, the Telomerase gene responsible for telomere length and stability, which triggers apoptosis via a caspase-dependent pathway. [14, 15 & 16].

Melatonin receptor 1B (MTNR1B), gene expresses the type 2 or MT-2 receptor and is found in many tissues and organs of the immune system. MT2 receptor, an intrinsic membrane protein, has a high-affinity interaction with an inhibitory G-protein and has been associated with altered melatonin signaling and secretion. An enhanced expression due to a common risk allele- G in the rs10830963 has been linked with alterations in intracellular melatonin signaling pathway in various cell types, which could disturb the biological circadian rhythm in individuals and these disturbances could enhance disease susceptibility. Genome-wide association studies also highlight the role of this gene in the pathogenesis of various diseases, including type 2 diabetes, myocardial infarction, polycystic ovary syndrome, and cancer.

The SNP rs10830963 is an intronic variant between exons 1 and 2. Studies suggest that rs10830963 C > G having the variant G-allele is associated with enhanced MTNR1B transcript levels in human β-pancreatic islets and the carriers expressing two to fourfold more mRNA transcripts. Studies and experimental findings suggest that increased MT2 protein levels exacerbate the inhibitory effect of melatonin on pancreatic insulin in risk allele carriers. Therefore, this polymorphism was associated with fasting blood glucose, fasting insulin homeostasis, and insulin resistance. Increased expression of MTNR1B on β cells has also been linked to diminished intracellular cyclic cAMP levels, thereby inhibiting insulin secretion, and the G-allele genotype results in higher MTNR1B protein levels. The variant was associated with fluctuations in FPG (Fasting Plasma Glucose) levels in nondiabetic individuals. MTNR1B exhibits its action by reducing insulin secretion via the formation of cGMP. Knock-out gene studies conducted in mice have confirmed the results by displaying a significant association between receptor variants and the decline in FPG levels. [17, 18, 19, 20, 21 & 22]. The effect of these hormone receptors in the context of leukemias and the risk conferred is under investigation in this study.

Materials and Methods

For this study a total of 201 cases of leukemic and preleukemic cases along with 201 controls were selected; patient history and consent along with details of biopsy smear examination were taken. The DNA isolation was done using the silica column method. The VDR gene (rs2228570) was analyzed using the RFLP method and the MTNR1B gene (rs10830963) was analyzed using the T- ARMS PCR method. The PCR was standardized using already published primers given below:

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VDR	F: 5′-AGCTGGCCCTGGCACTGAACTCTGGCTCT-3′ R: 5′- ATGGAAACACCTTGCTTCTTCTCCCTC-3' Restriction Digestion- FokI enzyme	CC- 267 bp CT- 267 bp 197+ 70 bp TT - 197+ 70 bp
MTNR1B	Fout: 5′- TTTTTGTGCTGCAAATGGGTTAAAGAGG-3′ Rout: 5′- GAGCCTTTGTTCAGAACCATGCTGCTTA-3′ Fin: 5′- CCAGTGATGCTAAGAATTCACACCATGTG-3′ Rin: 5′- CCAGGCAGTTACTGGTTCTGGATTGG-3′	Control- 439 bp CC-allele at 274 bp GG-allele at 220 bp CG- 439+ 274+220 bp

Both VDR (RFLP) and MTNR1B (T-ARMS PCR) were amplified at Initial denaturation at 94℃ 5 mins, Denaturation at 94℃ for 45 seconds, Annealing at 60℃ for 45 secs and extension at 72 ℃ for 1 min for 35 cycles with the final extension at 72 ℃ for 10 minutes. Amplified products MTNR1B were checked on 2 % agarose gel for allele specific amplification. The VDR products treated with FokI restriction enzyme, 16 hours digestion, were analyzed on 10% polyacrylamide gel.

Results & Statistical Analysis

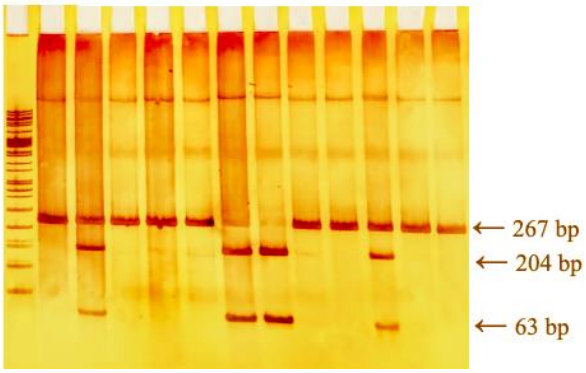

Figure 1A. Shows VDR FokI rs2228570 PCR- RFLP products on 10% PAGE gel, 267-bp CC, 204-bp and 63-bp TT genotypes, and 267 + 204 + 63 bp CT genotype.

VDR = 402	CC	CT	TT
CASES (201)	109	77	15
CONTROLS (201)	149	47	5

Table 1A. Frequency of Alleles for VDR FokI rs2228570

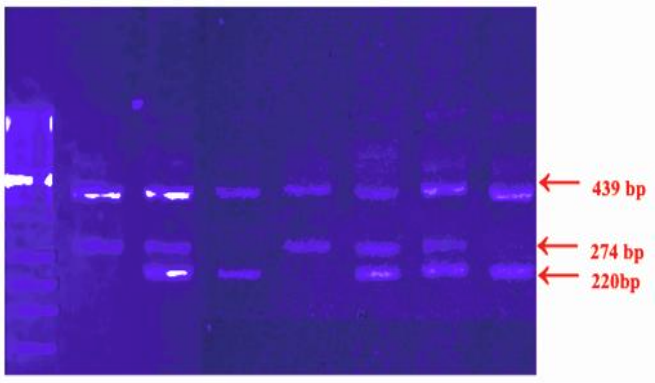

Figure 1B. Shows MTNR1B rs10830963 T-ARMS PCR products on 2% AGE gel, 439-bp Control Band, 274-bp CC and 220-bp GG, and 274 + 220 bp CG genotype.

MTNR1B = 402	CC	CG	GG
CASES (201)	79	83	39
CONTROLS (201)	74	103	24

Table 1B. Frequency of Alleles for MTNR1B rs10830963

Statistical Analysis

VDR gene SNP rs2228570 statistical analysis was carried out for Homozygous TT, CC & Heterozygous CT as follows (χ^2 trend =16.6370, ***p*-value = < 0.0001**, *d.f.*= 1; *RR* = 3.0000 (95 % C.I = 1.1113 to 8.0986), *z*-score = 2.168; ***p*-value = 0.0301**, rs2228570 TT- alleles); *RR* = 1.6383 (95% C.I =1.2069 to 2.2239), *z*-score = 3.166 , ***p*-value = 0.0015**, rs2228570 CT- Heterozygous); *RR*= 0.7315 (95% C.I = 0.6290 to 0.8508), *z*- score = 4.058, *p*-value = **< 0.0001,** CC- Homozygous).

MTNR1B gene SNP rs10830963 statistical analysis was carried out for Homozygous CC, GG & Heterozygous CG (χ^2 trend = 0.4167, *p*-value = 0.5186, *d.f.*= 1; *RR* =1.6250 (95% C.I =1.0162 to 2.5985) *z*-score = 2.027, ***p*-value = 0.0426,** - GG-Homozygous alleles); *RR* = 0.8058 (95% C.I= 0.6513 to 0.9971) z-score = 1.987, ***p*-value = 0.0469**, CG- Heterozygous); *RR* =1.0676 (95% C.I = 0.8317 to 1.3703) *z*- score = 0.513, *p*-value = 0.6077, CC- Homozygous).

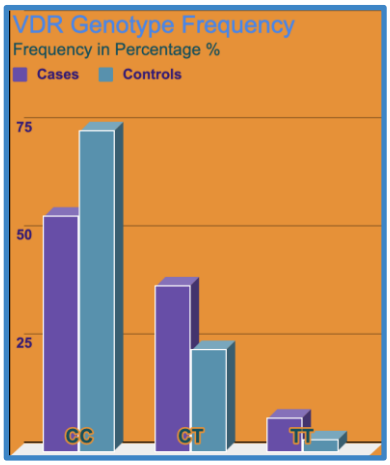

Figure 2A-Genotypic frequency % of the VDR gene.

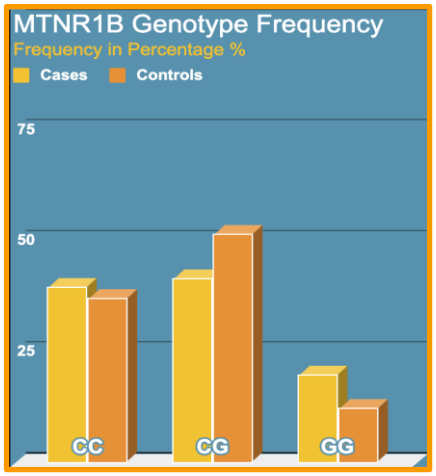

Figure 2B -Genotypic frequency % of the MTNR1B gene.

Figure 2A and Figure 2B Analyze the Genotypic Frequency Distribution Percentage- Analysis of the VDR rs2228570 genotypic distribution shows a higher percentage of homozygous CC alleles in control samples compared to the cases, and the frequency of heterozygous CT and homozygous TT is comparatively higher in cases compared to controls. Analysis of the MTNR1B genotypic distribution shows an almost similar distribution of the homozygous CC genotype in cases and controls. The percentage distribution of heterozygous CG genotype is higher in control samples compared to cases, and the percentage of homozygous GG genotype is more frequent in cases compared to controls.

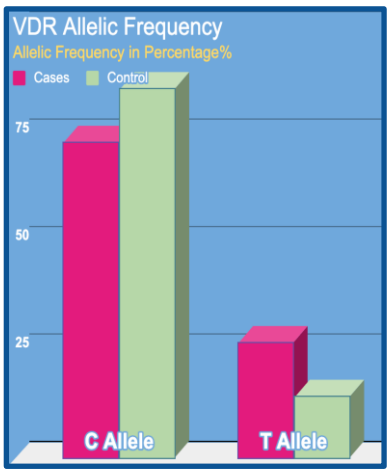

Figure 3A Allelic frequency % of VDR gene

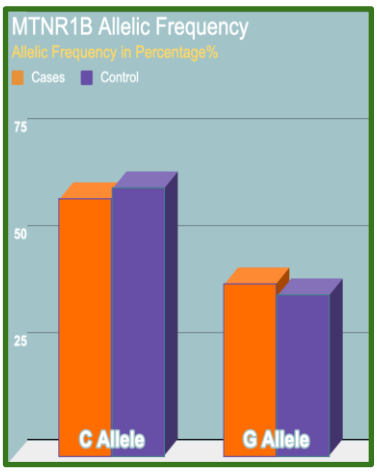

Figure 3B Allelic frequency % of MTNR1B gene

Figure 3A and Figure 3B Analyze the Allelic Frequency Distribution Percentage- The allelic frequency distribution for the VDR rs2228570 T > C analysis shows a higher percentage of the C-allele compared to the frequency of the T-allele in both cases and controls. The C-allele is more frequent amongst control samples compared to the cases, and the T-allele distribution is observed more frequently in cases compared to control samples. When comparing allelic frequency distribution for the MTNR1B gene C > G rs10830963 analysis, the C-allele is comparatively more frequent than the G-allele in both cases and controls. The distribution of the C-allele is quite comparable in cases and controls. The G-allele is more frequent amongst cases compared to the controls.

Discussion

New research has implicated that vitamin D deficiency is a critical factor in the pathology of various cancers. In the current study, we first analyzed the VDR gene for rs2228570 T > C polymorphism in pre-leukemic and leukemic cases. This study found the role of TT alleles rs2228570 to be significantly associated with increased risk for refractory aplastic anemia and pancytopenia (p-value <0.05), CT genotype frequency was also significantly higher in cases compared to controls (p-value <0.01) and could be associated with an elevated risk of leukemic transformation. According to a study, TT carriers of rs2228570 demonstrated poor response to treatment and an elevated risk of myelodysplastic syndrome and acute leukemic transformation [23 & 24]. An explanation for this association could be that individuals predisposed to deregulated Vitamin D pathways due to disease-associated gene sequence alterations could contribute to a decreased anti-inflammatory action in cells in response to Vitamin D stimulation. Thus, VDR FokI polymorphism could be a factor en route to immune dysfunction and leukemic transformation.

The other functional polymorphic variant analyzed in this study was C > G rs10830963 in the MTNR1B gene. We found the GG genotype significantly higher in the cases than in the control samples (p-value < 0.05). GG genotype is associated with a risk of developing Type-2 Diabetes, high plasma glucose levels, and irregular glucose homeostasis. This intronic variant results in enhanced expression of Melatonin type-2 receptors on pancreatic beta-cells and decreased serum melatonin levels. There are two explanations possible for understanding the potential contribution of this variation in the disease progression; firstly, the enhanced blood glucose levels could contribute to metabolic reprogramming in cells, and secondly, the melatonin receptor expression can alter the immune responses, diminishing anti-inflammatory action in preleukemic and leukemic conditions contributing to chronic inflammatory state which can fuel the malignant phenotype [25 & 26].

Conclusion

Vitamin D and melatonin share a complex relation, as both hormone levels depend on the duration, wavelength, and intensity of exposure to light. Vitamin D synthesis occurs in the presence of sunlight, in contrast to melatonin, as melatonin synthesis occurs during dark hours, so both can contribute to various circadian rhythm-regulated functions such as mood, sleep, and immunity [27]. Vitamin D behaves as a hormone and communicates with cells via its specific nuclear receptor, a crucial requirement for signaling activation to generate metabolic responses. The combined action of vitamin D and downstream VDR-RXR heterodimer expression stimulates a metabolic response at the cellular level. Receptor complex activation requires adequate concentrations of Vitamin D and other ligands. Therefore, the Vitamin D sufficiency triggered activation of VDR and subsequent complex formation is crucial for its functioning as a downstream regulator of gene expression and its further action in preventing progression in chronic age-related conditions and cancer [28 & 29]. Despite limitations regarding information related to Vitamin D serum levels, this study found a significant association between FokI polymorphism and pre-leukemic and leukemic cases initially presented as anemia. The truncated variant has an altered response to vitamin D stimulus, also known to be associated with reduced circulating levels of 25(OH)D. Thus, evidence from other studies also supports its potential role as a prognostic marker in both myeloblastic and lymphoblastic leukemias.

Melatonin partners with other metabolites and regulates oxidative stress via its action as a scavenger of toxic ROS, suppressing ROS production and activating antioxidant enzymes. Thus, it amplifies its potential as an anti-inflammatory signaling molecule. Further, it also helps in the functioning and maintenance of homeostasis within the mitochondria and contributes to the stability of the genome. Studies indicate that vitamin D and melatonin coordinate their functions. Coincidental decline of vitamin D and melatonin levels with age causes mitochondrial function impairment and can be a risk factor associated with various clinical conditions [30]. The timed actions of its pro-inflammatory and anti-inflammatory responses indicate the role of melatonin in regulating and fine-tuning inflammation during early and chronic phases. The MTNR1B variant can impact the immunomodulatory action of melatonin. Thus, it can be a reliable marker for screening individuals at risk of chronic inflammation and other associated diseases.

Isothermal titration calorimetry studies indicate that melatonin directly interacts via the ligand binding domains with the Vitamin-D Receptor, so VDR can function as a nuclear receptor for melatonin and could be a potential signaling molecule for circadian rhythms [31, 32 & 33]. FokI polymorphic variation in the N-terminal region of VDR could impact melatonin signaling via the VDR pathway. A possible explanation for its role could be that the variation changes the conformation of VDR, thus affecting its affinity towards melatonin, and it can alter its interaction with melatonin and the subsequent effects [34, 35 & 36].

The relevance of melatonin and Vitamin D supplementation in human health requires further detailed analysis. This study, combined with additional information from serum analysis, can help us explore the relationship between melatonin and Vitamin D serum levels and individual receptor polymorphism genotypes. Thus, it can work well to understand how individuals with receptor variants respond to these treatments. Combining vitamin D and melatonin supplementation may be beneficial in addressing oxidative stress imbalances. Whether the therapeutic combination of Vitamin D and Melatonin will help alleviate disease severity in cancer can only be determined if we understand the interplay of these genotypic variants and their ligands during chronic diseases.

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