RESEARCH ARTICLE

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Association of Selective *VDR* Gene Polymorphisms with Diffuse Large B-Cell Lymphoma (DLBCL) in a South Indian Population

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Abstract

Background: The prevalence of Diffuse Large B-Cell Lymphoma (DLBCL) in India ranges from 34% to 60%. The prognosis for DLBCL can vary widely depending on various factors, including vitamin D deficiency. Research suggests that low vitamin D levels may be linked to poor overall survival (OS) and progression-free survival (PFS) in DLBCL patients. Additionally, polymorphisms in the vitamin D receptor (*VDR*) gene, specifically the *BsmI* and *TaqI* alleles, have been significantly associated with disease prognosis. However, the association of *VDR* polymorphisms and vitamin D deficiency with DLBCL is yet to be explored. Therefore, this study aims to evaluate the association of *VDR* gene polymorphisms (*BsmI, TaqI, FokI, ApaI*) in DLBCL patients. **Methods:** In this cross-sectional study, 50 treatment-naive DLBCL patients from southern part of India were included. 100 samples of unrelated apparently healthy controls were used as comparator. Demographic characteristics of DLBCL patients were recorded and SNPs in *VDR* (real time polymerase chain reaction) were assessed. All analyses were performed using SPSS (V26). $P<0.05$ was considered statistically significant. **Results:** The frequencies of mutant genotypes [TT- *BsmI*, AG- *TaqI* and AG- *FokI*] were significantly associated with a reduced risk of DLBCL, decreasing the risk DLBCL by 71% (OR=0.29, 95% CI= 0.105 to 0.807), 72% (OR=0.28, 95% CI= 0.133 to 0.608) and 70% (OR=0.3, 95% CI= 0.07 to 1.225). Additionally, comparison with other Indian studies and ethnic groups revealed significant distinctions in *VDR* genotypes. Further, the haplotype analysis of SNPs in the *VDR* gene revealed significant association of C-A-G-T haplotype (rs731236-rs7975232-rs1544410-rs2228570) with the disease phenotype. **Conclusion:** The study shows significant association of *BsmI*, *TaqI*, and *FokI VDR* SNPs with DLBCL.

Keywords: DLBCL- vitamin D- *VDR* polymorphism- SNP- haplotype

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Introduction

Non-Hodgkin's lymphoma accounts for nearly 2.8% of the global cancer, leading to 2.6% of cancer-related deaths annually [1]. Diffuse Large B-Cell Lymphoma (DLBCL), represent 25% of Non-Hodgkin's Lymphoma, in Western populations [2]. In India, the prevalence of DLBCL ranges from 34% to 60% [3-5]. The Onco-Collect Lymphoma Registry from India has found DLBCL as the predominant lymphoma diagnosed at a median age of 57 years [6-7]. Vitamin D, also known as cholecalciferol has a pivotal role in bone health by regulating the balance of calcium and phosphorus [8-11]. Additionally, it contributes to cellular proliferation, angiogenesis, and regulation of gene expression, playing a crucial role in the growth and development of diverse malignancies, such as prostate, breast, bone, leukaemias, and lymphomas [12-13]. High vitamin D levels have been linked to a reduced incidence of cancers, including breast, colorectal, and prostate [14]. Vitamin D deficiency is associated with reduced Overall Survival (OS) and Event-Free Survival (EFS) in DLBCL patients [15-16]. Vitamin D synthesis primarily occurs in the skin through exposure to sunlight. Subsequent hydroxylation at positions 25 and 1 in the liver and kidney, respectively, results in the formation of its active metabolite, 1,25-dihydroxycholecalciferol [1,25(OH)D] [17-18]. Upon entering cells, this active vitamin D binds to the vitamin D receptor (*VDR*) encoded by the *VDR* gene and produces its actions [19]. The *VDR* gene is polymorphic, featuring variations such as *BsmI, TaqI, FokI*, and *ApaI* [20-21]. Substantial evidence supports the regulatory role of *VDR* in various signalling

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pathways, influencing processes such as apoptosis, autophagy, and cellular adhesion, with implications for the pathophysiology of leukaemia/lymphoma [22]. *VDR* also impacts the growth and proliferation of lymphocytes in the immune system by targeting immune modulators [23]. The association between variants like *TaqI, FokI*, and *BsmI* with specific types of non-Hodgkin's Lymphoma (NHL) has been established. While , the b allele of the *BsmI* polymorphism and the t allele of the TaqI polymorphism are associated with DLBCL, the f allele of the *FokI* polymorphism is linked to T-cell lymphoma [22]. However, the association of polymorphisms in the *VDR* gene with DLBCL has not been studied among Indian patients. Hence this study aimed to evaluate the association of single-nucleotide polymorphisms (SNPs) of the *VDR* gene (*BsmI, TaqI, FokI* and *ApaI*) with DLBCL susceptibility in patients from the southern part of India.

Materials and Methods

Study population

After obtaining Institutional Ethics Committee (IEC) approval, written informed consent was taken from DLBCL patients reporting at Regional Cancer Centre (RCC) JIPMER, Puducherry. Newly diagnosed cases of DLBCL based on the 2008 World Health Organization classification from south Indian origin (residing in South India for the past three generations and speaking any one of the South Indian languages as mother tongue) [24] aged between 18-80 years (inclusive), belonging to either gender, willing and able to provide written informed consent were included in the study from July 2020 to April 2024. Samples collected from 100 unrelated healthy South Indians from a previous study of the PI were used after getting institutional ethics committee approval. From eligible and willing participants, baseline details were collected apart from measuring height and weight. 3 ml of blood sample was collected from a peripheral vein for DNA extraction under aseptic conditions. The sample for DNA extraction was collected in tubes containing 100µl of 10% EDTA and were centrifuged at 2,500 rpm for 20 min following which cells with buffy coat were separated and DNA was extracted from peripheral leucocytes using the phenol-chloroform method quantified using Qubit, quality of DNA was assessed by OD 260/280 ratio and was diluted to a concentration of 50 ng/µL of DNA. Diluted DNA samples were stored in a deep freezer at a temperature of -80°C for future use.

Genotyping and assessment parameters

Genotyping of *VDR* (*BsmI*[rs1544410], *TaqI*[rs731236], *FokI*[rs2228570] and ApaI[rs7975232] polymorphic variants were performed using real-time polymerase chain reaction (RT-PCR) [QuantStudio™ 3 Real-Time PCR]. Thermofisher TaqMan SNP assay kits were used for genotyping of *VDR* polymorphisms as per the manufacturer's instructions. HaploView version 4.2 was used to carry out the haplotype-based association analysis. Haplotype frequencies as well as the linkage disequilibrium (LD) metrics R and D' were computed. The chi-squared test was used to compare the haplotype distribution between the case and control groups. The 10,000-fold permutation test was used to adjust significant p-values [25].

Statistical analysis

Continuous data were expressed as mean ± standard deviation. Categorical data including the frequency of genotypes were expressed as numbers and percentages. Bonferroni correction was done for multiple comparisons. After confirming that the population is in Hardy Weinberg Equilibrium, the chi-square test was used to compare the genotype distribution between cases and healthy controls. All the analyses were performed using SPSS (v26). $P<0.05$ was considered to be statistically significant.

Results

Fifty DLBCL cases were enrolled from the regional cancer centre (RCC) of JIPMER, a tertiary care hospital. There were 27 males and 23 females in the cases group and 41 males and 59 females among the control group. The mean (SD) value of the age of DLBCL cases was 52.36 ± 13.37 years as compared to 37.84±12.68 years respectively of the healthy controls. Of this, 34 were vitamin D deficient (<19 ng/ml) [12.65 ±3.91], 14 were vitamin D insufficient (20-29 ng/ml) [28.4 ±11.36] and 2 had normal vitamin D levels (>30 ng/ml) [92.5 ±39.39]. The baseline characteristics of DLBCL cases have been enumerated in Table 1.

Base pair changes and locations of the SNPs (*BsmI, TaqI, FokI, ApaI*) of the *VDR* gene included in the study are shown in Table 2. The distribution of genotypic

Table 1. Baseline Characteristics of Treatment Naive DLBCL Cases and Healthy Controls

Characteristics	Overall
DLBCL patients (n=50)	
n (%)	50 (100)
Age (years), mean ± SD	52.36 ± 13.37
Male	27 (54)
Female	23 (46)
Stage	
I	3 (6)
II	13 (26)
III	4 (8)
IV	30 (60)
Baseline calcium (mg/dL), mean ± SD	9.18±0.9
Ki 67 index mean ± SD	71.67±17.65
Healthy controls (n=100)	
n (%)	100 (100)
Age (years), mean ± SD	37.84±12.68
Male	41 (41%)
Female	59 (59%)
n (%)	

SD, Standard deviation; DLBCL, Diffuse Large B cell lymphoma

Table 2. List of Studied SNPs in Vitamin D Receptor Gene with rsIDs and Chromosome Locations

S.No.	SNP	rsID	Base pair change	Chromosome number	Chromosomal location
1	BsmI	rs1544410	T/C	12	Intron 8
2	TaqI	rs731236	G/A		Exon 9
3	FokI	rs2228570	A/G		Exon 2
4	ApaI	rs7975232	A/C		Intron 8

SNP, single nucleotide polymorphism; rsiD, rapid stain identification

frequencies (by Hardy Weinberg equilibrium) among cases and controls is depicted in Table 3.

Upon comparison of *VDR* genotypic frequencies between DLBCL cases and healthy controls using the chi-square test, a significant difference was observed with respect to *BsmI* (rs1544410), *TaqI* (rs731236) and *FokI* (rs2228570) polymorphisms.

The genotypes TT, AG, and AG of the *BsmI* (71%) (OR=0.29, 95% CI= 0.105 to 0.807), *TaqI* (70%) (OR=0.3, 95% CI= 0.07 to 1.225), and *FokI* (72%) (OR=0.28, 95% CI= 0.133 to 0.608) were associated with DLBCL. Also, a comparison of genotype frequencies of Vitamin D receptor polymorphism (*BsmI, TaqI, FokI, ApaI*) with other Indian populations and ethnic groups was assessed and significant differences in *VDR* genotype frequencies were observed (S-01 and S-02).

In haplotype analysis, the Linkage Disequilibrium (LD) patterns of the four *VDR* SNPs were assessed as given in Figure 1. The results of linkage disequilibrium

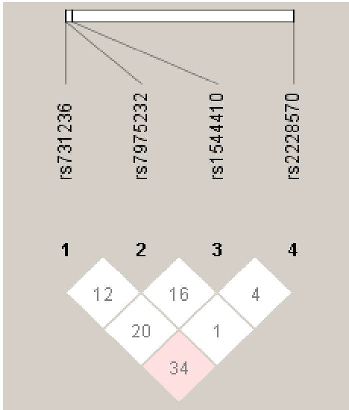

Figure 1. The LD Pattern of *VDR* rs731236, rs7975232, rs1544410, rs228570 Polymorphisms DLBCL Cases Vs Apparently Healthy South Indian Controls.

Table 3. Distribution of Genotype Frequencies of *VDR* Polymorphisms in DLBCL Cases and South Indian Healthy Controls (*BsmI, TaqI, FokI, ApaI*)

rsID	SNPs	DLBCL patients	Heathy controls	OR (95% CI)	p-value
BsmI rs1544410	Genotypes, n (%)	50 (100)	100 (100)		
	CC	12 (24)	38 (38)	Reference	
	TT	13 (26)	12 (12)	0.29 (0.105,0.807)	0.008*
	CT	25 (50)	50 (50)	0.63 (0.282,0.416)	0.132
	C	24 (48)	63 (63)		
	T	26 (52)	37 (37)	0.5 (0.273,1.078)	0.04*
TaqI rs731236	Genotypes, n (%)	50 (100)	100 (100)		
	AA	19 (38)	57 (57)	Reference	
	GG	4 (8)	20 (20)	1.66 (0.506,5.492)	0.2
	AG	27 (54)	23 (23)	0.28 (0.133,0.608)	0.0005*
	A	32 (64)	69 (69)		
	G	18 (36)	31 (31)	0.79 (0.39,1.635)	0.269
FokI rs2228570	Genotypes, n (%)	50 (100)	100 (100)		
	AA	3 (6)	12 (12)	Reference	
	GG	25 (50)	61 (61)	0.61 (0.158,2.348)	0.23
	AG	22 (44)	27 (27)	0.3 (0.077,1.225)	0.04*
	A	14 (28)	25 (25)		
	G	36 (72)	75 (75)	1.16 (0.543, 2.508)	0.34
ApaI rs7975232	Genotypes, n (%)	50 (100)	100 (100)		
	CC	14 (28)	27 (27)	Reference	
	AA	9 (18)	28 (28)	1.61 (0.599,4.343)	0.17
	AC	27 (54)	45(45)	0.86 (0.387,1.928)	0.36
	C	27 (54)	50 (50)		
	A	23 (46)	50 (50)	1.17 (0.59,2.31)	0.322

*P<0.05 considered significant; NS, Not significant; SNP, single nucleotide polymorphism

Table 4. Linkage Disequilibrium Across the Study SNPs

	rs731236	rs7975232	rs1544410	rs2228570
rs731236	-	0.122	0.209	0.342
rs7975232	0.01	-	0.165	0.011
rs1544410	0.022	0.005	-	
rs2228570	0.079	0	0.001	-

D' is shown above the diagonal' r2 is shown below the diagonal

Table 5. Haplotype Analysis of SNP Genotyped in *VDR* Gene

rs731236	rs7975232	rs1544410	rs2228570	Frequency (overall)	Frequency (case, control)	Chi square	p value	*p value
T	A			0.416	0.482, 0.283	10.911	0.001	0.0087*
C	A			0.257	0.203, 0.367	9.427	0.0021	0.0175*
T	G			0.167	0.148, 0.207	1.688	0.1939	0.7913
C	G			0.159	0.167, 0.143	0.296	0.5861	0.9914
	A	G		0.482	0.500, 0.446	0.755	0.385	0.9389
	G	G		0.255	0.245, 0.274	0.278	0.597	0.9925
	A	A		0.192	0.185, 0.204	0.142	0.706	0.9984
	G	A		0.072	0.070, 0.076	0.047	0.828	0.999
		G	T	0.384	0.375, 0.403	0.226	0.6349	0.9957
		G	A	0.352	0.370, 0.317	0.83	0.3624	0.9271
		A	A	0.134	0.135, 0.133	0.002	0.967	1.000
		A	T	0.129	0.120, 0.147	0.423	0.575	0.984
T	A	G		0.318	0.376, 0.204	9.09	0.0026	0.0242*
C	A	G		0.163	0.124, 0.241	6.611	0.0098	0.081
T	G	G		0.144	0.128, 0.176	1.238	0.2659	0.9076
C	G	G		0.111	0.117, 0.099	0.209	0.6475	0.9991
T	A	A		0.097	0.106, 0.079	0.567	0.4515	0.9909
C	A	A		0.095	0.079, 0.126	1.756	0.1852	0.7798
C	G	A		0.048	0.050, 0.043	0.068	0.7946	1.000
T	G	A		0.024	0.020, 0.032	0.382	0.5366	0.9975
	A	G	T	0.255	0.246, 0.273	0.262	0.6087	0.9997
	A	G	A	0.227	0.254, 0.173	2.521	0.1123	0.6121
	G	G	T	0.129	0.129, 0.129	0.000	0.9849	1.000
	G	G	A	0.126	0.117, 0.145	0.485	0.486	0.9954
	A	A	A	0.099	0.106, 0.086	0.279	0.5973	0.9996
	A	A	T	0.093	0.080, 0.118	1.172	0.2789	0.9267
	G	A	T	0.037	0.041, 0.029	0.249	0.6181	0.9997
	G	A	A	0.034	0.029, 0.046	0.61	0.4389	0.9904
T	A	G	A	0.162	0.186, 0.114	2.523	0.1122	0.6656
T	A	G	T	0.155	0.190, 0.087	5.388	0.0203	0.1612
C	A	G	T	0.096	0.055, 0.178	11.686	0.0006	0.0062*
T	G	G	A	0.093	0.076, 0.128	2.195	0.1385	0.7633
C	G	G	T	0.076	0.074, 0.079	0.026	0.8716	1.000
T	A	A	A	0.075	0.077, 0.072	0.029	0.8659	1.000
C	A	A	T	0.071	0.051, 0.112	3.754	0.5727	0.3801
C	A	G	A	0.066	0.069, 0.060	0.084	0.7715	1.000
T	G	G	T	0.053	0.054, 0.053	0.000	0.9824	1.000
C	G	G	A	0.035	0.043, 0.021	0.95	0.3297	0.9892
C	G	A	T	0.032	0.035, 0.026	0.178	0.6728	1.000
C	A	A	A	0.025	0.029, 0.017	0.408	0.5229	0.999
T	A	A	T	0.053	0.029, 0.011	0.956	0.3282	0.9891
C	G	A	A	0.016	0.015, 0.018	0.035	0.8526	1.000
T	G	A	A	0.014	0.011, 0.020	0.459	0.4982	0.9998

p value-chi-square test. *p value calculated using permutation test and a total of 10,000 permutations

(LD) tests noted as D' and r2 between studied locus in the *VDR* gene and the distribution of haplotype frequencies between cases and controls is shown in Tables 4 and 5.

Fifteen -four marker haplotypes with a frequency of >1% were detected. The best evidence of an association with DLBCL cases was observed with the CAGT haplotype, which was more frequent among controls than cases even after the permutation test (0.055,0.178, p=0.0062). The following three and two marker haplotypes were also found to be significantly more frequent in the cases: TAG (rs731236, rs7975232, rs1544410, p=0.0242), TA (rs731236, rs7975232, p= 0.0087), CA (rs731236, rs7975232, p = 0.0175).

Discussion

The present study has found an association between the presence of the *VDR* (*BsmI, TaqI* and *FokI*) gene polymorphisms in the south Indian patients with DLBCL for the first time (Table 3). In *BsmI, TaqI* and *FokI* (rs1544410, rs731236 and rs2228570), the mutant genotypes (TT, AG, AG) were found to have a significant association with DLBCL susceptibility. This is consistent with the study that showed an increased risk of DLBCL with *BsmI* B allele and *TaqI* t alleles within a population-based case-control study conducted in Australia [25]. However, the association of *FokI* and *ApaI* with DLBCL was not assessed in their study.

Comparisons with other Indian studies (S-01) and diverse ethnic groups (S-02) revealed variations in the distribution of *VDR* genotypes. These differences emphasize the importance of considering population-specific genetic variations in cancer susceptibility. In our study, the significant genetic variants (TAG (p=0.0242), TA (p=0.0087), CA(p=0.0015) and four marker CAGT haplotype (0.055 Vs 0.178, p=0.0062)) was shown to have association with DLBCL. These findings suggest that specific genetic variations in the *VDR* gene may contribute to the susceptibility of the disease.

Study conducted in the Chinese Han population concluded that *VDR* (*FokI*) rs2228570 and (*TaqI*) rs731236 polymorphisms may be important genetic factors in multiple myeloma susceptibility [26]. Likewise, another study in Iranian population found a significant association between *VDR* polymorphism *TaqI* and acute myeloid leukaemia [27]. However, in contrast, lack of association of *FokI, ApaI* and *TaqI* polymorphisms were observed with colorectal cancer in the Egyptian population [28].

Future studies should investigate these associations and their functional implications in various cancers to enhance our understanding of the disease mechanism. The limitation of the study is small sample size from a single centre. While polymorphisms of the *VDR* gene might play a role in the pathogenesis of DLBCL, the non-association of ApaI needs to be interpreted considering this limitation.

In conclusion, the study found that *BsmI*, *TaqI* and *FokI* of the *VDR* gene were associated with DLBCL in the south Indian population. Studies with larger sample sizes and Targeted *VDR* gene sequencing are warranted to validate this finding. Understanding these genetic associations may pave the way for further research and clinical applications in the context of lymphomas, particularly DLBCL.

Author Contribution Statement

AA and SS contributed to study design and concept. AA, LG, SS and PG were responsible for patient recruitment, data collection and verification. AA, SK and SS contributed to lab analysis, data entry and quality control. AA, SV, SS, PG and JM were involved in data analysis, interpretation and preparation of first draft. All authors contributed to data analysis, interpretation, writing and revision of the manuscript. All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

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Ethical approval
This study was started after obtaining approval from Institutional Ethics Committee for human studies, JIPMER, Puducherry.

Informed consent
Obtained from all individuals included in this study.

Conflict of interest
Nil.

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