LETTER to the EDITOR **Editorial Process:** Submission:06/14/2025 Acceptance:01/27/2026 Published:02/05/2026

VDR Gene Polymorphisms and Diffuse Large B-Cell Lymphoma: Correspondence

Asian Pac J Cancer Prev, **27 (2),** 401-402

Dear Editor

The publication on "Association of Selective *VDR* Gene Polymorphisms with Diffuse Large B-Cell Lymphoma (DLBCL) in a South Indian Population [1]" is interesting. This study is an intriguing attempt to link genetic anomalies (specifically, *VDR* gene polymorphisms) to the risk of diffuse large B-cell lymphoma (DLBCL) in a South Indian community. However, there are various limitations that may impair the reliability and interpretation of the findings. For example, the study's cross-sectional design does not allow for clear cause and effect, and the sample size of only 50 patients and 100 controls may be insufficient to draw population-level conclusions, particularly when performing complex genetic analyses that require larger sample sizes to account for genetic variability.

Questions to stimulate discussion include

Are the protective associations of mutant alleles, such as TT-BsmI and AG-TaqI with DLBCL risk the result of clear biological mechanisms, or are they simply statistical associations caused by sampling bias or linkage disequilibrium with other genes? Another question is whether the effects of these *VDR* polymorphisms correlate with vitamin D levels in the body, which is significant given that vitamin D levels were not examined in this sample.

Although the data show that some SNPs in the *VDR* gene are related with a lower incidence of DLBCL, further interpretations suggest that this association may result from a population-specific immunological variation mechanism rather than a direct effect of vitamin D. For example, the C-A-G-T haplotype identified to be associated with disease could be linked to the expression of genes that govern B- or T-cells at a deeper level than just vitamin D response. Furthermore, comparisons with other populations demonstrate the significance of ethnic context in genetic research.

This study concentrated on SNPs in the *VDR* gene; however, in relation to DLBCL a condition linked to immune dysfunction and cell division regulation it is conceivable that polymorphisms in other genes related to immunity, such as *IL-10, TNF-α, IL-6,* or those governing B-cell proliferation (e.g., *BCL2, MYC, P53*), could also be significant [2]. Failure to account for these polymorphisms may result in overlooking deeper connections between genetics and disease pathology. Moreover, prior research suggests that the *CYP27B1* and *CYP24A1* genes, which are involved in the synthesis and metabolism of vitamin D, may contribute to immune regulation through active vitamin D ($1,25(OH)_2D$) [3]. To achieve a more thorough understanding of the vitamin D and immune system, future studies should broaden their scope to include these genes.

To broaden the perspective, multivariate regression studies incorporating other characteristics such as age, gender, nutritional status, or body mass index should be conducted to see whether the effect of *VDR* polymorphisms remains significant when these covariates are controlled. Furthermore, measuring blood vitamin D levels in conjunction with SNP analysis will assist answer the critical question of whether the presence of a mutant allele impacts vitamin D activity in clinical settings. Finally, future research should use prospective cohort designs to better understand the long-term relationship between *VDR* polymorphisms and DLBCL prognosis.

References

1. Anandaradje A, Venkatraman S, Goenka L, Ganesn P, Tripathi SK, Mathaiyan J, et al. Association of selective *VDR* gene polymorphisms with diffuse large b-cell lymphoma (dlbcl) in a south indian population. Asian Pac J Cancer Prev. 2025;26(5):1761-6. https://doi.org/10.31557/apjcp.2025.26.5.1761.
2. Mellgren K, Hedegaard CJ, Schmiegelow K, Müller K. Plasma cytokine profiles at diagnosis in pediatric patients with non-hodgkin lymphoma. J Pediatr Hematol Oncol. 2012;34(4):271-5. https://doi.org/10.1097/MPH.0b013e3182431e02.
3. Kundu R, Chain BM, Coussens AK, Khoo B, Noursadeghi M. Regulation of cyp27b1 and cyp24a1 hydroxylases limits cell-autonomous activation of vitamin d in dendritic cells. Eur J Immunol. 2014;44(6):1781-90. https://doi.org/10.1002/eji.201344157.

Amnuay Kleebayoon[1], Viroj Wiwanitkit[2]*

*[1]Private Academic Consultant, Samraong, Cambodia. [2]Department of Research Analytics, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences Saveetha University, India. *For Correspondence: dramnuaykleebayoon@gmail.com*

Reply to the letter to the editor: VDR Gene Polymorphisms and Diffuse Large B-Cell Lymphoma: correspondence

Dear Editor

We thank you for the interest shown towards our article titled "Association of Selective *VDR* Gene Polymorphisms with Diffuse Large B-Cell Lymphoma (DLBCL) in a South Indian Population" and appreciate the suggestions provided for further discussion.

1. VDR gene association with DLBCL

Our findings suggest that polymorphisms in BsmI, TaqI, and FokI of the *VDR* gene may be associated with DLBCL in the south Indian population. We acknowledge that the cross-sectional design and the modest sample size of 50 patients and 100 controls warrant cautious interpretation of the association between SNPs and disease risk. We recognize the need for larger, multicentric studies and targeted sequencing of the *VDR* gene to validate these results. Nonetheless, our study results suggest an indication towards the possible role of *VDR* genes in disease association. These preliminary findings may help future studies aimed at establishing causality using a larger sample size and a cohort design.

2. Genes linked to vitamin D metabolic pathway

We appreciate the thoughtful suggestion to include other immune-regulatory genes, such as IL-6, IL-10, TNF-α, BCL2, MYC, and P53, in future genetic analyses. However, the present study, which was designed to explore the association of various polymorphisms in *VDR* gene, did not consider other immune regulated genes during conception, considering feasibility and financial constraints. That said, the suggestion is well taken and such an investigation could be conducted as an independent study in future. Further, as rightly pointed out about the genes linked to synthesis and metabolism of vitamin D to achieve thorough understanding of vitamin D, we have already completed a study in DLBCL patients with vitamin D pathway genes which is yet to be published.

3. Correlation of VDR polymorphisms with vitamin D level

As rightly pointed out, our findings suggest a statistically significant association between the SNPs (BsmI, FokI and TaqI) with DLBCL susceptibility. Similarly, Purdue et al. [1], reported association of FokI, BsmI and TaqI polymorphisms in *VDR* with few subtypes of NHL. Although such associations may occasionally be due to linkage disequilibrium with other functional variants or sampling variability, existing literature does support a functional role for *VDR* polymorphisms in DLBCL through modulation of immune responses, apoptosis, and cell proliferation, a process central to lymphomagenesis [2, 3]. However, further studies are required to explore whether genotype and haplotype associations are driven by population specific immunological variation mechanism rather than a direct effect of vitamin D.

4. Multivariate regression

We agree that adjusting for relevant covariates through multivariate regression would enhance the robustness of future analyses, allowing for a clearer understanding of whether *VDR* polymorphisms independently contribute to DLBCL risk. Nevertheless, this was not attempted in our study due to the small sample size.

5. Future research

We agree that future research employing a prospective cohort design and whole genome sequencing will provide a better understanding of the association between genetic polymorphisms and DLBCL susceptibility.

References

1. Purdue MP, Lan Q, Kricker A, Vajdic CM, Rothman N, Armstrong BK. Vitamin d receptor gene polymorphisms and risk of non-hodgkin's lymphoma. Haematologica. 2007;92(8):1145-6. https://doi.org/10.3324/haematol.11053.
2. Denzer N, Vogt T, Reichrath J. Vitamin d receptor (*VDR*) polymorphisms and skin cancer: A systematic review. Dermatoendocrinol. 2011;3(3):205-10. https://doi.org/10.4161/derm.3.3.16519.
3. Campbell MJ, Trump DL. Vitamin d receptor signaling and cancer. Endocrinol Metab Clin North Am. 2017;46(4):1009-38. https://doi.org/10.1016/j.ecl.2017.07.007.

Annuja Anandaradje, Sandhiya Selvarajan*

Department of Clinical Pharmacology, JIPMER, Puducherry.
**For Correspondence: sandhiyaselvarajan@gmail.com*