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Autoimmunity eventuates when the immune system attacks self-molecules as a result of the breakdown in immune tolerance. Vitiligo is an autoimmune skin-disfiguring disease characterized by depigmented macules on the skin caused due to destruction of functional melanocytes. Targeting autoimmune diseases *via* immunomodulation has become an essential strategy in today's era. A B7 superfamily member immune checkpoint, the V-set domain containing T-cell activation inhibitor-1 (VTCN1, also known as B7-H4, B7S1, and B7x), is an immune checkpoint involved in inhibition of T cell activation. *VTCN1* transcript has been reported in various lymphoid and non-lymphoid tissues, but its protein expression is restricted, indicating its translational regulation. Dysregulation of VTCN1 has resulted in the exacerbation of various autoimmune diseases. Nardilysin (NRD1), a metalloproteinase, cleaves membrane-tethered VTCN1 resulting in the shedding of soluble-VTCN1 (sVTCN1). However, the role of VTCN1 and NRD1 in vitiligo pathogenesis is unexplored. In the present study we have investigated the genetic association of *VTCN1* intronic polymorphisms (rs10923223 T/C and rs12046117 C/T) with vitiligo susceptibility in Gujarat population using 411 vitiligo patients and 450 controls with the help of Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP), estimated *VTCN1 & NRD1* transcript levels from peripheral blood mononuclear cells (PBMCs) of 188 vitiligo patients and 12 skin samples by real-time PCR, estimated sVTCN1 and NRD1 protein levels from 84 generalized active vitiligo patient's plasma by ELISA, estimated VTCN1 protein levels in the 12 lesional, perilesional and non lesional skin samples of vitiligo patients by immunofluorescence and performed immunophenotypic analysis of VTCN1 from the blood of generalized active vitiligo patients. The analysis revealed increased *VTCN1* and *NRD1* transcript levels in the vitiliginous skin, increased sVTCN1 and NRD1 levels in the plasma, and decreased VTCN1 protein levels in the skin of vitiligo patients as compared to healthy controls. The genetic analysis did not find significant association of *VTCN1* intronic polymorphisms rs10923223 T/C and rs12046117 C/T with vitiligo susceptibility in Gujarat population. However, significant decrease in the percentage of VTCN1-positive CD4, CD8, and regulatory T cells (Tregs) was observed in vitiligo patients. Interestingly, we found a significant increase in $CD69^+$ activated T cells of vitiligo patients along with significantly decreased $CD8^+CD69^+VTCN1^+$ cells. Overall, our findings showed altered VTCN1 and NRD1 expressions in the blood and skin of vitiligo patients, suggesting their potential role in the development and progression of vitiligo. Furthermore, a significant reduction in VTCN1-positive CD4, CD8, Treg cells, and dendritic cells in vitiligo patients indicates the breakdown in self-tolerance. This collapse may provoke autoreactive T cells and generate an exacerbated response towards healthy melanocytes that ultimately cause melanocyte destruction and aid to vitiligo progression. The findings of this study provide new insight into immune dysregulation reported in vitiligo and may lead to the development of new therapeutic strategies using an immunomodulatory approach to cure it.