A comprehensive review on vitamin D receptor (VDR) gene polymorphism in immune-related diseases with emphasis on dermatologic disorders

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There are many immune mediated disorders with the corroborated role of vitamin D or Vitamin D Receptor (VDR) gene polymorphisms in their pathogenesis, immunologic regulation, and disease characteristics. Therefore, in this review, we searched PubMed data base in regard to the role of VDR gene polymorphisms in common autoimmune disorders, emphasizing on dermatologic diseases.

Keywords: vitamin D, genetic polymorphism, autoimmune diseases

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INTRODUCTION

Numerous studies have evaluated the association between the inheritance of VDR gene polymorphisms such as FokI polymorphism and genetic susceptibility to various illnesses, including cancers, and infectious, inflammatory, and immunogenic disorders. There are many studies on such type of association in autoimmune or immune-related disorders such as type 1 diabetes mellitus [1-10], multiple sclerosis [11-14], autoimmune thyroid diseases [15-22], autoimmune hepatitis and liver diseases [23], inflammatory bowel diseases [24,25], collagen vascular disorders [26-29], and many specific dermatologic entities, including psoriasis [30-37], alopecia areata [38-40], recurrent aphthous stomatitis [41], vitiligo [42], and skin cancers [43-47]. Despite the body of work done on this subject, an obvious and conclusive association is yet to be identified. There are no similar studies focused on immunobullous disorders in the field of dermatology.

There are many studies regarding vitamin D levels and their association with different aspects of immunobullous disorders such as pemphigus vulgaris; however, we did not find any studies on the relationship between vitamin D receptor gene polymorphisms and these entities. In some studies, lower levels of vitamin D were found in pemphigus vulgaris patients irrespective of their age, BMI, and sun exposure. This could be associated with disease severity and worsening. Or vitamin D deficiency could be a predisposing factor in PV through affecting immune system (TGF-β/IL-17), particularly regulatory T cells. However, an inverse association was also reported between vitamin D levels and severity of immunobullous disorders (these patients had hypovitaminosis D, increased rate of vertebral fracture, and normal BMD) [48-53]. There are many articles regarding VDR gene polymorphisms in psoriasis [30-37]. Moreover, a recent meta-analysis showed that circulating 25(OH) D levels were lower in patients with psoriasis, and there was a small statistically significant and negative correlation between psoriasis severity and 25(OH)D levels [54].

METHOD

In this review, summarized in Table 1, the role of vitamin D receptor gene polymorphism in immune-related non-dermatologic and dermatologic disorders was studied. PubMed data base in

Table 1. The role of Vitamin D Receptor gene polymorphism in common immune-related non-dermatologic and dermatologic disorders

Disorder	Study	Findings
Common autoimmune disorders		
Diabetes mellitus [2,3, 5-10, 55-66]	Fassbender et al., 2002	There was a correlation between the TT genotype and diabetes in Germans. No difference was found in bone turnover markers.
	Mohammadnejad et al., 2012	VDR TaqI polymorphism was connected with DM type 1 in an Iranian population.
	Sahin et al., 2012	FasL -843C/T and VDR FokI gene polymorphisms and type 1 diabetes were associated in Turkey but not Fas -670A/G.
	Pani et al., 2000	There was a linkage between VDR or a nearby gene and DM type 1 susceptibility in Germans.
	Nejentsev et al., 2004	Common sequence variation of VDR gene had no major effect on DM type 1.
	Zemunik et al., 2005	An association was reported between VDR FokI polymorphism and several VDR and IL-1-R1 haplotypes in DM type 1 in Dalmatians.
	Capoluongo et al., 2006	There was slight increase in the prevalence of “ff” VDR genotype in DM type 1.
	Chang et al., 2000	Vitamin D receptor gene polymorphisms were correlated with type 1 diabetes in a Taiwanese population.
	Turpeinen et al., 2003	No association was seen between single nucleotide polymorphisms in VDR gene and type 1 diabetes in a Finnish population.
	Abd-Allah et al., 2014	VDR BsmI and FokI polymorphisms were associated with vitamin D deficiency in DM type 1 in Egyptian children.
	Boraska et al., 2008	There existed relationships between specific VDR gene variants and DM type 1 in South Croatia.
	Lemos et al., 2008	Single nucleotide polymorphisms of the VDR gene had no significant role in DM type 1 in a Portuguese population.
	Mauf et al., 2015	Genotypes of the VDR and CYP24A1 in susceptibility to DM type 1 might influence the immune modulatory effects of 25 (OH) D3.
	Morán-Auth et al., 2015	A more balanced T cell immunity could be beneficial for patients with DM type 1 carrying the “FF” genotype as an adequate vitamin D therapy.
	Mory et al., 2009	No relationships were found between VDR polymorphisms and beta-cell autoimmunity. However, age and remaining beta-cell function were correlated in Brazilian individuals with DM type 1.
	Panierakis et al., 2009	FokI, BsmI, ApaI, and TaqI polymorphisms of the VDR gene were associated with DM type 1 prevalence in a southern European population.
	Qin et al., 2014	VDR BsmI B allele, bb genotype was correlated with DM type 1 risk in Asians, and bb genotype was associated with its risk in the overall populations.
	Skrabić et al., 2003	VDR polymorphisms had a relationship with increased risks of DM type 1 in a Dalmatian population of South Croatia.
	Tizaoui et al., 2014	In DM type 1 pathogenesis, VDR polymorphisms interacted with each other and the environmental factors.
	Zhang et al., 2012	BsmI polymorphism was associated with increased risks of DM type 1, particularly in Asians.
Diabetes mellitus and Thyroid dysfunction [67]	Mory et al., 2016	The VDR FokI polymorphism (rs10735810) was associated with the persistence of GADA (glutamic acid decarboxylase antibody), TPOA positivity (TPO Antibody) and TD (thyroid dysfunction) in Brazilians with DM type 1. Positivity to TPOA and VDR polymorphism FokI was greatly associated with the concurrence of DM type 1 and TD.
Thyroid dysfunction [15-22, 68-70]	Feng et al., 2013	The cumulative effect of BsmI or TaqI polymorphisms in VDR had a meaningful association with AITD (autoimmune thyroid diseases).
	Ban et al., 2000	There was a relationship between Graves’ disease and a VDR polymorphism in the Japanese; also, a VDR-FokI polymorphism might affect bone mineral metabolism as a predictor of osteoporosis risk as a complication of Graves’ disease in remission.
	Abd El Gawad et al., 2012	BsmI, ApaI, and TaqI polymorphisms in the VDR gene were associated with susceptibility to GD (Graves’ disease) whereas BsmI, ApaI, and TaqI polymorphisms were not correlated with serum levels of 1,25 (OH)2D3.

Table 1. Continued

Disorder	Study	Findings
	Zhou et al., 2009	ApaI, BsmI and FokI polymorphisms in the VDR gene were associated with susceptibility to GD (Graves' Disease) in Asian populations while ApaI, BsmI, TaqI, and FokI polymorphisms had no correlation with GD in Caucasian populations.
	Chen et al., 2007	The VDR-FokI T/C polymorphism could possibly be employed as a genetic marker for predicting the likelihood of (Graves' disease) development.
	Ramos-Lopez et al., 2005	An association was seen between VDR gene polymorphisms and Graves' disease in the German and Polish populations, but not in the Serbian ones. VDR polymorphisms were differentially distributed in the three populations. Therefore, VDR polymorphisms analysis should be interpreted according to the population background.
	Stefanić et al., 2005	There was a relationship between VDR gene BsmI/ApaI/TaqI polymorphisms and Graves' disease susceptibility in a subset of patients from Eastern Croatia. The ApaI, BsmI "AA", "BB" genotypes, and combined "BBAAtt" genotype were revealed to allow protection against Graves' disease; however, ApaI "aa" and TaqI "TT" genotypes were associated with an increased risk of GD.
	Ban et al., 2000	There was an association between the VDR gene and Graves' disease in a Japanese population; therefore, VDR gene could be a non-HLA-linked gene predisposing an individual to GD.
	Lin et al., 2006	Chinese patients in Taiwan carrying the C/C homozygote of the VDR-FokI gene polymorphism in exon 2 could run a higher risk of HT (Hashimoto's thyroiditis).
	Stefanić et al., 2008	Common haplotypic variants within the VDR gene 3'-region, previously linked with VDR mRNA expression and allelic imbalance, could also be associated with Hashimoto's thyroiditis in the general population and disease pathogenesis.
	Yazici et al., 2013	VDR gene TaqI TT and FokI FF genotypes were associated with increased risks of Hashimoto's thyroiditis in Turkish patients. BbAaTtFf genotype seemed to be protective for HT disease in our population.
Multiple sclerosis [11-14, 71-77]	Huang and Xie, 2012	The VDR Apa-I, Bsm-I, Fok-I and Taq-I polymorphisms were not associated with MS risk.
	Sioka et al., 2011	Aq-I and Bsm-I polymorphisms of the VDR gene were not related to MS risk, BMI, or BMD in the studied Greek population.
	Orton et al., 2011	There was no direct connection between vitamin D metabolism genes and MS susceptibility despite the large sample size and comprehensive gene coverage.
	Smolders et al., 2009	No association existed between the Fok-I VDRG polymorphism and MS.
	Agliardi et al., 2011	There was interaction between the major genetic (HLA-DRB*15) and environmental (vitamin D) factors associated with MS onset.
	Bettencourt et al., 2017	There was a relationship between FokI ff genotype and MS susceptibility, but not its form or progression.
	Čierny et al., 2015	They found a weak association between VDR SNP FokI, and the MS risk in women
	Cox et al., 2012	There was a weak evidence of an association between a common variation within the VDR gene and MS in the largest study reported to date.
	García-Martín et al., 2013	VDR rs2228570 and rs731236 polymorphisms were not related to the risk of MS; therefore, there was no interaction between these VDR SNPs and HLADRB1 regarding MS risk.
	Kalman and Toldy, 2014	It was revealed that there were very complex molecular networks underlying inflammatory demyelination disorder and the roles of vitamin D and other environmental factors.
	Yamout et al., 2016	No connection was observed between serum vitamin D or A or VDR genotypes and MS. HLA-DRB1*15 was the major factor leading to more than 3-fold higher risks for developing MS among a Lebanese population.
Liver disorder [23,107-110]	Fan et al., 2005	A genetic connection existed between VDR polymorphisms and autoimmune liver diseases such as AIH (autoimmune hepatitis) and PBC (primary biliary cirrhosis) in Chinese patients.
	Fan et al., 2003	There was a significant correlation between FokI polymorphism and AIH as well as between the BsmI polymorphisms and PBC in a Chinese population.

Table 1. Continued

Disorder	Study	Findings
	Kempinska-Podhorodecka et al., 2017	The ApaI polymorphisms in VDR might impact disease-related symptoms and the quality of life in patients with PSC (primary sclerosing cholangitis).
	Tanaka et al., 2009	The genotype 'BB' and 'B' allele at BsmI polymorphism of the VDR gene could affect the risk of PBC development.
	Vogel et al., 2002	There existed a link between genetic of VDR polymorphisms and autoimmune liver diseases such as PBC and AIH in German patients.
Inflammatory Bowel Disease (IBD) [24,25,82-88]	Simmons et al., 2000	There was a genetic association between Crohn's disease susceptibility and Vitamin D receptor gene polymorphisms such as TaqI polymorphism.
	Naderi et al., 2008	There existed the likelihood of a relationship between Fok I polymorphism in VDR receptor gene and Crohn's susceptibility in an Iranian population.
	Hughes et al., 2011	Common variations in the VDR gene alone had no significant effect on the predisposition to IBD in an Irish population.
	Wang et al., 2014	ApaI polymorphism might increase the risk of CD (Crohn's disease); in contrast, TaqI polymorphism might reduce the risk of UC, particularly in Caucasians.
	Xia et al., 2014	Their study showed that genetic polymorphism of VDR (Fok I, Bsm I, Apa I, Taq I) and the serum levels of 25 (OH) D were significantly linked with UC (ulcerative colitis). Mutation of VDR (Bsm I) was a protective factor for UC. Moreover, mutant genotype (TC/CC) of VDR (Fok I) and vitamin D deficiency might exert synergistic effects on the susceptibility to UC.
	Xia et al., 2015	The mutation of FokI gene influenced the severity of the disease in UC patients. The AAC haplotype formed by the VDR BsmI, ApaI and TaqI gene might reduce UC attack risk.
	Xia et al., 2016	Vitamin D receptor (BsmI, ApaI, and TaqI) mutations and lower 25 (OH)D levels were correlated with CD in Chinese patients. VDR (FokI, ApaI, and TaqI) mutations and vitamin D deficiency might have a combined impact on CD.
	Xue et al., 2013	The meta-analysis showed a major increase in CD risk in Europeans carrying TaqI tt genotype and a significant decrease in CD risk in all carriers of the ApaI "a" allele. Regarding Asians, the VDR FokI polymorphism was shown to present susceptibility to UC. Concerning males, the TaqI tt genotype was associated with susceptibilities to both UC and CD.
	Zheng et al., 2017	VDR polymorphisms and 25 (OH) D level were significantly connected with UC risk and severity in a Chinese Han population.
Collagen vascular disorders [26-29,89-94]	Lee et al., 2011	This meta-analysis showed that the VDR FokI polymorphism might confer susceptibility to RA in Europeans. Furthermore, associations were found between the VDR BsmI polymorphism and susceptibilities to SLE and LN (lupus nephritis) in Asians.
	Mao and Huang, 2014	BsmI B allele might be a risk factor for SLE onset among the overall populations and Asians; also, FokI FF genotype was a risk factor for SLE susceptibility in Asians.
	Xiong et al., 2014	BsmI and FokI polymorphism were related to increased risk of SLE, especially in an Asian population.
	Zhou et al., 2015	BsmI B allele and bb genotype, Fok1 f allele and ff genotype were connected with the risk of SLE in the overall populations; in Asians, however, these associations were not reported in Caucasians.
	Hitchon et al., 2012	VitD receptor polymorphisms might affect the high prevalence of RA in North American Native populations.
	John et al., 2017	An association was observed between rs1544410 and RA in Pakistani samples.
	Kamal et al., 2016	VDR gene polymorphisms were significantly associated with Behçet's disease in Egyptian patients.
	Maalej et al., 2005	F allele and F/F VDR genotypes were associated with RA.
	Song et al., 2016	The meta-analysis suggested that the VDR FokI polymorphism was associated with susceptibility to RA in European populations.
	Tizaoui et al., 2015	TaqI and FokI VDR polymorphisms were significantly related to RA risk.
Dermatologic Disorders		

Table 1. Continued

Disorder	Study	Findings
Psoriasis [30-37]	Acikbas et al., 2012	Certain haplotypes of VDR were important in resistance to vitamin D3 therapy and the onset of psoriasis.
	Polić et al., 2012	None of the analyzed polymorphisms was individually associated with the risk of psoriasis, diabetes or combined phenotype development.
	Liu et al., 2013	In this meta-analysis, ApaI and TaqI polymorphisms in VDR gene were revealed to be associated with psoriasis in Caucasians.
	Lee et al., 2012	VDR ApaI polymorphism contributed to susceptibility to psoriasis in a Turkish population. In addition, a relationship was found between the BsmI polymorphism and susceptibility to psoriasis in Asians and between the Fok I polymorphism and psoriasis in a Turkish population.
	Zuel-Fakkar et al., 2011	There was no significant prevalence of ApaI and TaqI genotypes of vitamin D receptor in Egyptian patients with psoriasis.
	Park et al., 1999	Allelic variance in the vitamin D receptor gene itself or other genes in linkage disequilibrium with this gene could make to prone to the development of psoriasis.
	Stefanic et al., 2013	No VDR gene variant showed a robust and reproducible correlation with risk for psoriasis.
	Vega-Hernandez et al., 2015	Polymorphisms FokI, ApaI, BsmI, and TaqI in the VDR gene were not connected with the risk of presenting psoriasis in a Mexican population; however, the TT (ff) genotype of the FokI polymorphism was significantly more prevalent in patients with the late onset of PsV (after age 40) and those without nail affection.
Alopecia areata [38-40]	Akar et al., 2007	No association was observed between VDR gene polymorphism and alopecia areata.
	Akar et al., 2004	No relationship was found between VDR gene polymorphism and AA, the VDR FokI polymorphism.
	Ates, 2017	VDR gene polymorphisms could not contribute to determin genetic susceptibility to AA.
Recurrent Aphthous Stomatitis (RAS) [41]	Bazrafshani et al., 2002	The inheritance of specific gene polymorphisms for TNF-alpha, TNF-beta or VDR did not seem to be a major factor in determining susceptibility to minor RAS.
Vitiligo [42, 95, 96]	Li et al., 2012	There was a connection between VDR polymorphisms and 25 (OH)D levels, and there existed a genetic predisposition for vitiligo in a Chinese population.
	Aydıngöz et al., 2012	VDR TaqI gene polymorphism and the haplotype BsmI/ApaI/ TaqI/FokI/ Cdx2 GCCCG might be considered as a novel risk factor in vitiligo.
	Doss et al., 2015	Vitamin D deficiency had an effect on the extent of vitiligo and might have a role in the pathogenesis of vitiligo through its immunomodulatory role and its role in melanogenesis.
Skin cancer [43-47, 97-107]	Hutchinson et al., 2000	Polymorphisms of the VDR gene, which might lead to impaired function, were related to susceptibility and prognosis in melanoma.
	Li et al., 2007	Genetic variants (TaqI t protective allele and FokI f risk allele) in VDR might change the risk of melanoma.
	Randerson-Moor et al., 2009	Vitamin D and VDR seemed to slightly but potentially contribute to melanoma susceptibility, and putatively play a greater role in disease progression.
	Mocellin et al., 2008	There was a connection between 1 VDR gene polymorphism (BsmI) and the risk of developing melanoma.
	Burns et al., 2017	Benefits of early treatment and prevention of NMSC with chemopreventive agents (for those with the BsmI SNP) were shown. A screening for the BsmI SNP might confirm the importance of sun protection and assist skin cancer prevention, thereby reducing skin cancer burden.
	Lee et al., 2015	This meta-analysis demonstrated that the VDR BsmI polymorphism was associated with susceptibility to melanoma in Europeans, suggesting that carrying the VDR BsmI B allele might be a protective factor against melanoma development.
	Orlow et al., 2012	The VDR might greatly contribute to melanomagenesis.
	Orlow et al., 2016	VDR gene might affect melanoma survival; however, the mechanism by which VDR exerts its effect did not seem to be run by tumor aggressiveness.

Table 1. Continued

Disorder	Study	Findings
	Santonocito et al., 2007	BsmI polymorphism might play a role as a possible risk marker for MM and its aggressiveness.
	Zeljic et al., 2014	FokI and TaqI polymorphisms in the VDR gene might be potential biomarkers for melanoma susceptibility.
	Denzer et al., 2011	Vitamin D endocrine system (VDES) was important for pathogenesis and progression of MM and other skin cancers.
	Han et al., 2007	The polymorphisms were likely to have a role in MTHFR and VDR interacting with dietary intakes of folate and vitamin D in skin cancer development, particularly regarding SCC.
	Köstner et al., 2012	VDR polymorphisms were shown to be of importance for the development of BCCs and cutaneous SCCs.
	Lesiak et al., 2011	Certain VDR and MTHFR gene polymorphisms increased the risk of BCC development in individuals of Polish origin.
	Liu et al., 2005	VDR f and t alleles and their genotypes might protect against SCC of the head and neck.
	Reichrath et al., 2013	This study showed how vitamin D endocrine system (VDES) could be associated with tumorigenesis, prevention, and treatment of NMSC.

regard to the role of VDR gene polymorphisms in common autoimmune disorders, emphasizing on dermatologic diseases was searched.

RESULTS AND DISCUSSION

In this review, summarized in Table 1, the role of Vitamin D Receptor gene polymorphism in immune-related non-dermatologic and dermatologic disorders was studied.

CONCLUSION

There are many articles about the role of VDR gene receptor polymorphisms in common immune-mediated dermatologic and non-dermatologic disorders. These articles may propose various genetic susceptibilities to these disorders and their better management. There are no studies focused on this type of polymorphism; however, the role of vitamin D level have been frequently evaluated regarding different aspects of these diseases.

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