



Research article

The impact of genetic variants related to vitamin D and autoimmunity: A systematic review

Luisa Menezes Trefilio ^{a,b,1}, Letícia Bottino ^{a,c,1}, Rafaella de Carvalho Cardoso ^{a,d},
Guilherme Carneiro Montes ^{a,d}, Fabrícia Lima Fontes-Dantas ^{a,d,*}

^a Universidade Estadual do Rio de Janeiro, Instituto de Biologia Roberto Alcântara Gomes, Departamento de Farmacologia e Psicobiologia, Rio de Janeiro RJ, Brazil

^b Universidade Federal do Estado do Rio de Janeiro, Instituto Biomédico, Rio de Janeiro RJ, Brazil

^c Universidade Federal do Estado do Rio de Janeiro, Escola de Medicina, Rio de Janeiro RJ, Brazil

^d Universidade Estadual do Rio de Janeiro, Programa de Pós-Graduação em Fisiopatologia Clínica e Experimental, Rio de Janeiro RJ, Brazil

ARTICLE INFO

Keywords:

Vitamin D
Autoimmune diseases
Genetic variants
Susceptibility
And outcomes

ABSTRACT

Over the past few years, there has been a notable increment in scientific literature aimed at unraveling the genetic foundations of vitamin D signaling and its implications for susceptibility to autoimmunity, however, most of them address isolated diseases. Here, we conducted a systematic review of genetic variants related to vitamin D and autoimmune diseases and we discussed the current landscape of susceptibility and outcomes. Of 65 studies analyzed, most variants cited are in vitamin D binding protein (VDBP; rs2282679 GC gene), 25-hydroxylase (rs10751657 CYP2R1), 1 α -hydroxylase (rs10877012, CYP27B1) and the nuclear hormone receptor superfamily [FokI (rs2228570), BsmI (rs1544410), ApaI (rs7975232), and TaqI (rs731236) in VDR gene]. Therefore, our findings confirmed the associations of several genetic variants of vitamin D signaling with a broad spectrum of autoimmune diseases/traits. In addition, given the low number of papers found with functional analysis, further studies to elucidate the real effect that the variants exert on Vitamin D signaling are recommended.

1. Introduction

The indispensable Vitamin D (Vit D), is a precursor to steroid hormones and plays a crucial role in various physiological processes. There has been a documented rise involved to inadequate levels of this vitamin within the general population, making it a major public health problem [1]. Historically, Vit D has been associated with the regulation of blood calcium and phosphorus levels, as well as the mineralization of bone [2]. Furthermore, new evidence has demonstrated its important role in modulating the immune response [3–5]. Chemically, Vit D is a derivative of a steroid and the main physiologically relevant forms are vitamin D₂, present in plants and commonly referred to as ergocalciferol (or calciferol), and vitamin D₃, derived from animal tissues and denoted as cholecalciferol [6]. In the context of human physiology, 25-hydroxyvitamin D₃ (25[OH]D₃) serves as a stable indicator of Vitamin D status, and vitamin D₃

* Corresponding author. Universidade Estadual do Rio de Janeiro, Instituto de Biologia Roberto Alcântara Gomes, Departamento de Farmacologia e Psicobiologia, Rio de Janeiro RJ, Brazil.

E-mail addresses: luisatrefilio@edu.unirio.br (L.M. Trefilio), leticiaabottino@edu.unirio.br (L. Bottino), cardoso.rafaella@posgraduacao.uerj.br (R. de Carvalho Cardoso), guilherme.montes@uerj.br (G.C. Montes), fabricia.fontesdantas@uerj.br, fontesfl@hotmail.com (F.L. Fontes-Dantas).

¹ These authors contributed equally to this work.

demonstrates superior efficacy in sustaining its circulatory levels when compared to Vitamin D₂ [7,8]. Interestingly, twin studies suggest the variability in 25(OH)D₃ concentrations is highly heritable [9,10].

The metabolism of vitamin D₃ into 25(OH)D₃ (also called calcidiol) in the liver by 25-hydroxylase enzymes namely CYP2R1 and CYP27A1, and then hydroxylated by CYP27B1 in the kidneys to most potent derivative of Vit D: calcitriol (1,25-dihydroxycholecalciferol [1,25(OH)₂D₃]) [11]. At the cellular level, calcitriol regulates gene expression by interacting with the Vit D receptor (VDR). In the nucleus, this complex binds DNA in a heterodimer with the Retinoid X receptor (RXR) to enhance transcription via a vitamin D responsive element (VDRE) present within the promoter region of several target genes [12], including *HLA-DRB1* gene [13, 14].

The interaction between calcitriol and VDR in immune cells trigger the secretion of the antibacterial peptide cathelicidin for bacterial lysis [4]. [15]. However, overall, Vit D has multiple immunosuppressant properties. Calcitriol, in a VDR-dependent manner, is capable of inhibiting the self-renewal and differentiation of human dendritic cells [16,17]. Additionally, the expression of pro-inflammatory cytokines, including IFN γ , TNF α , IL-12, IL-17 and IL-21 are also suppressed by calcitriol [18–22].

Vit D affects the balance of CD4 T lymphocytes by decreasing the differentiation of Th1 and Th17 cells and promoting the proliferation of Th2 and T regulatory cells (Tregs) [23–25]. Also is necessary for the development of natural killer T (NKT) cells and regulate the production of IL-4 and IFN- γ by these cells [26]. Regarding the humoral immune response, Vit D can inhibit the proliferation and differentiation of B cells, as well as the production of antibodies, but promotes the generation of memory B cells with class switching [27].

Despite the difficulty of interpreting the publications, some studies have demonstrated inadequate Vit D intake, environmental factors (for instance, inadequate sunlight exposure, smoking and others), and deficient supplementation could potentially play a role in the onset and advancement of autoimmune disorders and increased susceptibility to infectious diseases [28–32]. Skin type is one of the main individual factors that predispose individuals to vitamin D deficiency. However, it is important to highlight that genetic determinants (such as genetic polymorphisms) have been increasingly studied and related to susceptibility to infection and autoimmune diseases [33]. Genome wide association studies (GWASs) have shown a common network of different variants for autoimmune diseases and the cooperative network of single-nucleotide polymorphisms (SNPs) appears to be the way to understand the complexity of these diseases [34]. Given the shared genetic susceptibility among autoimmune diseases, we conducted a systematic review on genetic variants related to Vit D signaling and autoimmune diseases or different outcomes.

2. Methods

2.1. Study design

This systematic review was conducted independently by two investigators (L.M.T and L.B) in accordance with Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) protocol for relevant inclusions and exclusions [35]. This study was registered in PROSPERO (ID CRD42022369473), <https://www.crd.york.ac.uk/prospERO/>. The focused question addressed was “If some genetic variants related to Vit D may be relevant in the susceptibility or different outcomes of autoimmune diseases”. To identify studies relevant to the focused question, we searched in PubMed, LILACS, SciELO, Cochrane and Scopus databases using the terms “Vitamin D” and “Autoimmune Diseases” and “Genetic Variants”, which were standardized by the MeSH database [36]. The databases were searched in all available period until December 2022.

After our first screening, we found 140 articles from PubMed, 2 articles from Cochrane, 63 Scopus, 0 from LILACS and SciELO (Flowchart 1). Then, a more careful evaluation was carried out following the inclusion criteria adapted according to Najjar et al. [37], including: 1) Population: human of any gender and age, race, and geographical distribution; 2) Association genetic studies; 3) Study design: genetic association, cohort, cross-section, case-control, and Mendelian randomization (MR) studies, as well as clinical trials, 4) Larger sample size (more than 100 participants). Review articles, clinical reports, consensus statements, duplicate studies, papers that were not written in English, editorials, and conference papers were excluded from the analysis. Furthermore, the research was not carried out in Preprints databases. After eliminating duplicates, the principal investigators (L.M.T and L.B) reviewed all titles and abstracts. Discordant results were resolved by a third author (F.L.F.D).

2.2. Data acquisition

Data acquisition was carried out using a modified table template previously published by Najjar et al. [37]. For this review paper, the data extracted were: first author; publication year; country/region where the study was carried out; autoimmune disease type; study design characteristics; the number of cases and controls studied; mean age of participants; genotyping methods; genotype distribution; adjusted factors; and the main results. After evaluation of all articles and data extraction by the two main authors, three other authors (R.C.C, F.L.F.D or G.M.) made the quality assessment of eligible studies using the Critical Appraisal Skills Program tools (<https://casp-uk.net/casp-tools-checklists/>, accessed in January of 2023).

3. Results

Initially, 205 potential studies were identified from the search. Of these, 33 studies were excluded because they were in duplicate. For the remaining 96 papers, we included 5 articles due data availability. Then, after the full text assessment it was identified that 36 papers did not meet the eligibility criteria, resulting in 65 studies analyzed.

Table 1
Characteristics of observational studies evaluating the association between vitamin D genetic variants and Autoimmune diseases included.

Autoimmune disease	Author; Year	Country	Study Design	N Case/Controls	Mean Age of Cases/ Controls (Year)	Methodology of variants identification	Adjusted Factors	Gene	Studied Variants	Relevant Key Findings
Multiple Sclerosis	Irizar, H., 2012 [177]	Spain	Case-Control	364/513	44.14 ± 13.02/50.17 ± 13.26	PCR-RFLP	Sex, DRB1*15:01 and ethnic origin	VDR	Apal (rs7975232) and TaqI (rs731236)	No association was found between VDR polymorphisms and MS, but a light tendency of Apal variants and MS had observed in the Basques ethnic group
Multiple Sclerosis	Agnello, L., 2017 [178]	Italy	Cohort Study	100/92	39,6 ± 10.3/ 45,2 ± 9.6	PCR-RFLP	No	GC and CYP27B1	GC (rs7041 and rs4588) and CYP27B1 (rs118204009, rs118204011 and rs118204012)	There was no difference in the distribution of GC and CYP27B1 genetic variants between the case and control groups.
Multiple Sclerosis	Karaky, M., 2016 [38]	Italy and Northern and Western European Ancestry in Utah	Cohort Study	109	NA	TaqMan Genotyping Assay	No	METTL1	rs10877013	Monocytes and B cells (LCLs) isolated from patients that carried the T allele (rs10877013) were able to increase the expression of CYP27B1 and VDR after stimulation.
Multiple Sclerosis	Cox, MB., 2012 [39]	UK and Australia	Case-Control and trio family dataset	727/604 1153 trio family dataset	NA	TaqMan Genotyping Assay	No	VDR	FokI (rs2228570) and TaqI (rs731236)	The C allele of rs731236 have a higher frequency in MS in the combined case-control and trio family dataset. The FokI variant was associated with multiple sclerosis only when combined with the presence of the DRB1*1501 tagging.

(continued on next page)

Table 1 (continued)

Autoimmune disease	Author; Year	Country	Study Design	N Case/Controls	Mean Age of Cases/ Controls (Year)	Methodology of variants identification	Adjusted Factors	Gene	Studied Variants	Relevant Key Findings
Multiple Sclerosis	Scazzone, C., 2018 [181]	Italy	Case-Control	105/130	39 ± 10/44 ± 9.9	TaqMan Genotyping Assay	Sex	NADSYN1 and CYP2R1	NADSYN (rs3829251, rs7944926 and rs12785878) and CYP2R1 (rs10741657 and rs10766197)	The minor allele A of rs10766197 was substantially higher in cases than in controls. 'AA' homozygotes tended to have lower 25-OH-vitamin d levels than 'GG' homozygotes or heterozygotes. AA was most present in men with MS and related with disease progression. None NADSYN polymorphisms were associated with MS.
Multiple Sclerosis	Lin, R., 2014 [40]	Australia	Cohort study	169	47,8	Illumina Infinium Hap370CNV array	Sex	WT1	rs10767935 and rs5030244	The SNPs rs10767935 and rs5030244 in WT1 modified the effects of IFN-β on 25 (OH)D levels and MS relapse. Individuals with at least one minor allele of rs10767935 and using IFN-β had higher levels of vitamin D. At rs5030244, carriers of the homozygous major allele (TT) who used IFN-β had higher 25(OH)D. In the dominant homozygotes of rs10767935 or with at least one copy of the recessive

(continued on next page)

Table 1 (continued)

Autoimmune disease	Author; Year	Country	Study Design	N Case/Controls	Mean Age of Cases/ Controls (Year)	Methodology of variants identification	Adjusted Factors	Gene	Studied Variants	Relevant Key Findings
Multiple Sclerosis	Al-Temaimi, RA., 2015 183 [41]	Kuwait	Case-Control	50/50	33.44 ± 9.63/ 28.68 ± 7.98	TaqMan Genotyping Assay	No	VDR	<i>FokI</i> (rs2228570), <i>BsmI</i> (rs1544410), <i>Apal</i> (rs7975232) and <i>TaqI</i> (rs731236)	rs5030244, there was no interaction between IFN-β and 25(OH)D The G allele of the <i>TaqI</i> genotype was related to the risk of MS, but <i>TaqI</i> did not influence vitamin D levels The <i>BsmI</i> C allele associating with MS risk, while the <i>Apal</i> and <i>FokI</i> genotypes did not show any association.
Multiple Sclerosis	García-Martín, E, 2013 [184]	Spain	Case-Control	303/310	43.9 ± 11.4/ 43.4 ± 11.7	TaqMan Genotyping Assay	Age at onset and gender	VDR	<i>FokI</i> (rs2228570) and <i>TaqI</i> (rs731236)	The frequencies of <i>FokI</i> and <i>TaqI</i> in patients and controls did not show differences, nor were they influenced by sex. Was not observed interaction between <i>HLA DRB1</i> *1501 with SNPs in <i>VDR</i> gene.
Multiple Sclerosis	Čierny, D., 2016 [42]	Slovak Republic	Case-Control	270/303	NA	PCR-RFLP	Sex and age	VDR	<i>Apal</i> (rs7975232), <i>BsmI</i> (rs1544410) and <i>TaqI</i> (rs731236)	<i>Apal</i> and <i>TaqI</i> polymorphisms were not associated neither with MS development nor with the disease progression. In this population, the <i>BsmI</i> BB (AA) genotype is linked to decreased susceptibility to MS.
Multiple Sclerosis	Ramagopalan, SV., 2011 [43]	United Kingdom	Case-Control	3564/1873	NA	TaqMan Genotyping Assay	Ethnicity	<i>CYP27B1</i>	rs118204009	First, one affected individual from 43 families were sequenced.

(continued on next page)

Table 1 (continued)

Autoimmune disease	Author; Year	Country	Study Design	N Case/Controls	Mean Age of Cases/ Controls (Year)	Methodology of variants identification	Adjusted Factors	Gene	Studied Variants	Relevant Key Findings
Multiple Sclerosis	Dickinson, J.L., 2009 [187]	Australia	Case-Control	136/235	43,5/43,6	PCR-RFLP	Sun exposure	VDR	TaqI (rs731236), FokI (rs10735810) and Cdx-2 (rs11574010).	In whole exome sequencing was found a rare variant in the <i>CYP27B1</i> gene. For validation, genotyping analysis was performed in case and controls. The rs118204009 SNP was not found in healthy controls. None significant association between the alleles frequencies for evaluated polymorphisms and cases of MS was found. Already the Cdx-2 showed an increase risk of MS among 'GG' homozygotes compared to 'AA' for those cases reporting low winter sun exposure during childhood.
Multiple Sclerosis	Barizzzone, N., 2013 [188]	Italy and Belgium	Familial study and Case-Control	134 families and 2608/1987	NA	Sanger sequencing and TaqMan Genotyping Assay	Sex and age	<i>CYP27B1</i>	rs118204009	No evidence was found that <i>CYP27B1</i> variants are functional for Multiple Sclerosis.
Multiple Sclerosis	Dwyer, T., 2008 [189]	Australia	Case-Control	136/272	43.5 (9.3)/ 43.6 (9.2)	Sequenom Autoflex Mass spectrometer	No	<i>MC1R</i>	Arg151Cys (rs1805007), Arg160Trp (rs1805008) and Asp294His (rs1805009)	Only Arg160Trp was associated with increased risk of MS. The association between <i>MC1R</i> and MS was increase among those with greater sun exposure.

(continued on next page)

Table 1 (continued)

Autoimmune disease	Author; Year	Country	Study Design	N Case/Controls	Mean Age of Cases/ Controls (Year)	Methodology of variants identification	Adjusted Factors	Gene	Studied Variants	Relevant Key Findings
Multiple Sclerosis	Tajouri, L., 2005 [44]	Australia	Case-Control	104/104	NA	PCR-RFLP	Age, sex and ethnicity	VDR	FokI (rs10735810), TaqI (rs731236) and ApaI (rs7975232)	HLA-DR15 effect did not alter the frequency of the other SNPs studied. The TaqI variant was significantly different between the case group and the control group, and the allelic association was more significant than the genotypic one. The study demonstrates that the rarer 't' allele is predominant in MS patients when compared to the control group and, in addition, it is suggested that carriers of the 't' allele are at least 2-fold more likely to have MS. A significant difference was also observed for the allelic distribution of ApaI, although the genotype distribution was not different. The FokI variant showed no association.
Multiple Sclerosis and Neuromyelitis optica	Zhuang, JC., 2015 [191]	China	Case-Control	149 (MS) and 110 (NMO)/294 healthy controls	NA	MassARRAY system and Sanger sequencing	No	CYP27B1 and CYP24A1	CYP27B1 (rs12368653, rs10876994, rs118204009 and rs703842) and CYP24A1 (rs2248359)	The variant p. R389H (rs118204009) had not been found. AC genotype of rs10876994 was much lower in NMO patients than

(continued on next page)

Table 1 (continued)

Autoimmune disease	Author; Year	Country	Study Design	N Case/Controls	Mean Age of Cases/ Controls (Year)	Methodology of variants identification	Adjusted Factors	Gene	Studied Variants	Relevant Key Findings
										the controls (32.7% and 46.9%), which indicate a possible protective role of A/C. In addition, the frequency of A/G alleles in rs703842 polymorphism is unequal in MS cases and control, in particular the A allele has been elevated in patients of MS, but this genotype and rs10876994 had statistical difference in NMO cases and controls. With regard about rs12368653, identified differences between MS cases and control, and cases of MS and NMO. None statistical significance in allele or genotype frequency of rs2248359 between any group. In carriers of MC1R:rs1805008 (T), who reported increased sensitivity toward sunlight, lower latitude was associated with higher MRI activity, whereas for noncarriers
Multiple Sclerosis	Ostkamp, P 2021 [45]	Germany	Cohort Study	883	32.43 (26.76–41.15)	Illumina OmniExpress chip	Age, sex, BMI, smoking, alcohol consumption, clinical subtype, neurological site of first manifestation, month of assessment, and center	MC1R	rs1805008, rs2228479 and rs885479	(continued on next page)

Table 1 (continued)

Autoimmune disease	Author; Year	Country	Study Design	N Case/Controls	Mean Age of Cases/ Controls (Year)	Methodology of variants identification	Adjusted Factors	Gene	Studied Variants	Relevant Key Findings
Multiple Sclerosis	Scazzone C, 2019 [193]	Italy	Case-Control	107/133	39,8 ± 9.9/44 ± 9.9	TaqMan Genotyping Assay	No	<i>Klotho</i>	rs1207568 and rs9536314	there was less MRI activity at lower latitudes. Allelic and genotypic frequencies did not differ between and multiple Sclerosis patients and controls, and any effect on disease course.
Multiple Sclerosis	Scazzone C, 2021 [194]	Italy	Case-Control	106/113	39/40	TaqMan Genotyping Assay	Sex	<i>FOXP3</i> and <i>GATA3</i>	<i>FOXP3</i> (rs3761547 and rs3761548) and <i>GATA3</i> (rs3824662)	The findings did not show any association among <i>FOXP3</i> and <i>GATA3</i> SNPs, vitamin D3, and MS susceptibility.
Sistemic Lupus Erythematosus	Mostowska A, 2013 [46]	Poland	Case-Control	258/545	40/39	PCR–RFLP	No	<i>VDR</i>	<i>FokI</i> (rs2228570), <i>BsmI</i> (rs1544410), <i>Apal</i> (rs7975232) and <i>TaqI</i> (rs731236)	The study did not observe significant differences for either the <i>VDR FokI</i> , <i>BsmI</i> , <i>Apal</i> and <i>TaqI</i> genotype and allele frequencies in patients with SLE and healthy individuals. However, the studied <i>VDR FokI</i> variant might increase the risk of some clinical presentations in patients with SLE.
Sistemic Lupus Erythematosus	Meza-Meza MR, 2022[47]	Mexico	Cross-sectional study	194/196	38/NA	TaqMan Genotyping Assay	No	<i>VDR</i>	<i>FokI</i> (rs2228570), <i>BsmI</i> (rs1544410), <i>Apal</i> (rs7975232), and <i>TaqI</i> (rs731236)	The study did not observe significant differences in the genotypic frequencies of the <i>VDR</i> variants between SLE patients vs. Control subjects. However, SLE

(continued on next page)

Table 1 (continued)

Autoimmune disease	Author; Year	Country	Study Design	N Case/Controls	Mean Age of Cases/ Controls (Year)	Methodology of variants identification	Adjusted Factors	Gene	Studied Variants	Relevant Key Findings
Systematic Lupus Erythematosus	Azab SF, 2016 [197]	Egypt	Case-Control	100/100	11,5/	PCR-RFLP	Age, sex and ethnicity	VDR	<i>BsmI</i> (rs1544410)	patient carriers of the TT <i>FokI</i> genotype showed higher clinical disease activity scores Patients who carry the 'BB' genotype are more susceptible to SLE and have high risk to development nephropathy.
Systemic Lupus Erythematosus	Mahto H, 2018 [48]	India	Case-Control	331/2822	27,4/29,56	PCR-RFLP	No	VDR	<i>FokI</i> (rs2228570), <i>TaqI</i> (rs731236), <i>BsmI</i> (rs1544410) and <i>Apal</i> (rs7975232)	Prevalence of <i>FokI</i> (Ff) and <i>TaqI</i> (Tt) heterozygotes were significantly higher in SLE patients compared to healthy controls. Furthermore, the minor alleles of <i>FokI</i> (f) and <i>TaqI</i> (t) polymorphisms were also more frequent in SLE patients than healthy controls.
Systemic Lupus Erythematosus	Monticielo AO, 2012 [[49]	Brazil	Case-Control	195/201	NA	PCR-RFLP	Phototype, ethnicity, age, gender, smoking status, BMI, hydroxychloroquine use, current corticosteroids use and vitamin D supplementation	VDR	<i>BsmI</i> (rs1544410) and <i>FokI</i> (rs222857)	There was no statistically significant difference in genotype and allelic frequencies of <i>BsmI</i> and <i>FokI</i> polymorphisms between European-derived cases and controls. According to genotype distribution, 25 (OH)D concentrations were significantly higher in patients

(continued on next page)

Table 1 (continued)

Autoimmune disease	Author; Year	Country	Study Design	N Case/Controls	Mean Age of Cases/ Controls (Year)	Methodology of variants identification	Adjusted Factors	Gene	Studied Variants	Relevant Key Findings
Systemic Lupus Erythematosus	Ozaki, Y., 2000[50]	Japan	Case-Control	58/87	NA	PCR-RFLP	Ethnicity	VDR	BsmI (rs1544410)	carrying the <i>FokI</i> f/f genotype compared with patients carrying the F/F genotype reinforcing its role in the functional activity of VDR. The 'B' allele was more frequent in the group of patients with SLE. Furthermore, the 'bb' genotype was associated with progression of the nephrotic syndrome in SLE patients.
Systemic Lupus Erythematosus	Silva, J.A., 2022 [51]	Brazil	Case-Control	128/138	37.1/33.5	TaqMan Genotyping Assay	Sex, age, ethnic group and same geographical area of the patients	VDR	TagSNPs (rs11168268, rs2248098, rs1540339, rs4760648 and rs3890733), <i>FokI</i> (rs2228570) and Cdx-2 (rs11568820)	The G allele of rs11168268 (A > G) and the G/G genotype were associated with increased susceptibility to SLE. However, the G allele of rs2248098 (A > G) and the A/G and G/G genotypes were associated with lower susceptibility to SLE. SNPs rs11168268 and rs2248098 were associated with the development of SLE.
Type 1 Diabetes	Ramos-Lopez, E., 2007[52]	Germany	Case-Control	284/294	NA	PCR-RFLP	No	CYP2R1	rs12369784, rs12794714, rs11023376, rs1257735 and rs10741657	rs12794714 is not associated with type 1 diabetes, but the 'G' variant of rs10741657 has a strong association and is

(continued on next page)

Table 1 (continued)

Autoimmune disease	Author; Year	Country	Study Design	N Case/Controls	Mean Age of Cases/ Controls (Year)	Methodology of variants identification	Adjusted Factors	Gene	Studied Variants	Relevant Key Findings
Type 1 diabetes	Panierakis, C., 2009[53]	Greece	Case-Control	100/96	NA	PCR-RFLP	No	VDR	<i>FokI</i> (rs2228570), <i>BsmI</i> (rs1544410), <i>Apal</i> (rs7975232), and <i>TaqI</i> (rs731236)	most transmissible from parents to affected children. Patients with this polymorphism have a titer of less than 25(OH)D3. The G allele is often associated with susceptibility to type 1 diabetes, on the other hand the 'A' allele may be protective. <i>FokI</i> , <i>BsmI</i> , <i>Apal</i> and <i>TaqI</i> polymorphisms are associated with type 1 diabetes, differing strongly between the case group and the control group. Cases were less commonly <i>FokI</i> F and <i>BsmI</i> B alleles, and more commonly <i>Apal</i> A and <i>TaqI</i> T alleles.
Type 1 Diabetes	Fichna, M, 2010 [54]	Poland	Case-Control	215/236	NA	PCR-RFLP	No	<i>PTPN22</i> , <i>PDCD1</i> and <i>CYP27B1</i>	<i>PTPN22</i> (rs2476601 and rs2488457), <i>PDCD1</i> (rs11568821) and <i>CYP27B1</i> (rs10877012) 98 VDR SNPs	Just <i>PTPN22</i> T1858 allele was significantly more frequent in T1DM compared to the control group.
Type 1 Diabetes	Nejentsev, S, 2004 [205]	United Kingdom and USA	Case-control and Cohort study	1587/1827 and 458 U K. families and 307 U S. families	NA	Invader (Third Wave Technologies, Madison, WI), TaqMan Genotyping Assay or Illumina Array	No	VDR	98 VDR SNPs	In general, in the study of families four SNPs, rs4303288, rs11168275, rs12721366, and rs2544043, showed evidence of association with type 1 diabetes.

(continued on next page)

Table 1 (continued)

Autoimmune disease	Author; Year	Country	Study Design	N Case/Controls	Mean Age of Cases/ Controls (Year)	Methodology of variants identification	Adjusted Factors	Gene	Studied Variants	Relevant Key Findings
Type 1 Diabetes	Bailey, R., 2007 [206]	United Kingdom	Case-Control and Cohort study	7854/8758 +2774 families	NA	TaqMan Genotyping Assay and Sanger sequencing	No	CYP27B1 and CYP24A1	CYP27B1 (rs10877012, rs4646536 and rs8176345) and 70 SNPs of CYP24A1	Nonetheless, no strong evidence was found between VDR and type 1 diabetes after validation of the findings in the case-control study. It was evidenced that the common C allele of rs10877012 is associated with T1D in the case group and in the evaluated families. The major T allele of the rs4646536 SNP was also related to the disease, unlike previous studies that failed to find such a relationship. CYP24A1 was not associated with disease during testing and did not show any evidence of risk.
Type 1 Diabetes	Miettinen, ME., 2015 [55]	Finland	Case-Control	474/348	NA	TaqMan Genotyping Assay	Month of sample collection	VDR; GC; CYP2R1; CYP27B1; CYP24A1; CYP27A1; CUBIN and NADSYN1/ DHCR7	VDR (rs731236, rs1544410, rs731236, rs7975232, rs2228570, rs4516035 and rs10783219); GC (rs4588, rs7041, rs12512631, rs2282679, rs3755967, rs17467825 and rs2298850); CYP2R1 (rs10741657,	Just VDR rs1544410, rs731236, rs4516035, rs1544410 and rs731236 had different genotype distributions between the case and control mothers and may influence the in utero environment and thus contribute to the early programming of

(continued on next page)

14

Autoimmune disease	Author; Year	Country	Study Design	N Case/Controls	Mean Age of Cases/ Controls (Year)	Methodology of variants identification	Adjusted Factors	Gene	Studied Variants	Relevant Key Findings
Type 1 Diabetes	Boraska, V., 2007 [208]	Croatia	Cohort Study	Case–parent trio samples: 132 parent–offspring trios, 20 parent–offspring duos, seven families with two affected children and one family with three affected children	NA	PCR-RFLP	No	VDR	rs2060793, rs1993116, rs7116978, rs12794714 and rs10500804); CYP27B1 (rs108770112 and rs4646536); CYP24A1 (rs6013897); CYP27A1 (rs17470271); CUBN (rs3740165); and NADSYN1/DHCR7 (rs12785878, rs3829251, rs7944926, rs12800438, rs3794060, rs4945008 and rs4944957) FokI (rs10735810), TaqI (rs731236), BsmI (rs1544410) and Tru9I (rs757343)	An association was found between Tru9I, in the Tru9I-BsmI haplotype and T1D in the population evaluated, from southern Croatia. In addition, there is a supertransmission of the major G allele of Tru9I between parents and offspring. The frequencies of the Asp/Glu and Glu/Glu were significantly increased in diabetic subjects with detectable IA-2 antibodies
Type 1 Diabetes	Ongagna, JC., 2005 [209]	France	Case-Control	110/68 and 115 first-degree relatives	Patients 25.1 years (range = 2–52 years) and control group matched for age; First-degree	PCR-RFLP	No	GC	Asp416Glu (rs7041)	The frequencies of the Asp/Glu and Glu/Glu were significantly increased in diabetic subjects with detectable IA-2 antibodies

(continued on next page)

Table 1 (continued)

Autoimmune disease	Author; Year	Country	Study Design	N Case/Controls	Mean Age of Cases/ Controls (Year)	Methodology of variants identification	Adjusted Factors	Gene	Studied Variants	Relevant Key Findings
Type 1 Diabetes	Ramos-Lopez, E., 2004 [210]	Germany	Cohort Study	187 families (561 subjects) with at least one affected offspring with T1D	relatives, 23 were siblings (age 20 ± 14 years), 36 were children (age 19 ± 12 years), and 56 were parents (age 37 ± 8 years). NA	SSCP Analysis and PCR-RFLP	No	CYP27B1	rs10877012 and rs4646536	The haplotype CT (rs10877012/rs4646536) was significantly more often transmitted to affected offspring, while the AT (rs10877012/rs4646536) showed a reduced transmission and might therefore be a protective factor in type 1 diabetes mellitus.
Type 1 diabetes	Van der Slik, AR., 2007 [56]	Netherlands	Case-Control	277/286	NA	PCR-SSP	Age	RXRB	rs1547387	The genotype and allelic frequencies of RXRB (rs1547387) showed no statistical difference between the group of patients and the group of controls. However, segregation with different HLA class II haplotypes may influence susceptibility to T1D
Type 1 Diabetes	Ferraz, R.S., 2022 [57]	Brazil	Case-Control	65/83	27.28 ± 10.3/ 38.49 ± 13.55	Sanger Sequencing	Sex, age and ancestry	VDR	Apal (rs7975232); BsmI (rs1544410); TaqI	No association was found between the variants and the risk of type 1 diabetes in this

(continued on next page)

Table 1 (continued)

Autoimmune disease	Author; Year	Country	Study Design	N Case/Controls	Mean Age of Cases/ Controls (Year)	Methodology of variants identification	Adjusted Factors	Gene	Studied Variants	Relevant Key Findings
Type 1 Diabetes	Almeida, J 2020 [213]	Portugal	Case-Control	350/490	29 ± 11.1/ 32,2 ± 11.2	PCR-RFLP and TaqMan Genotyping Assay	Sex and age	DHCR7, GC, CYP2R1 and CYP24A1	(rs731236); FokI (rs2228570)	population. T1DM patients who had the AA genotype of the rs1544410 variant or the CC genotype of rs731236 had lower serum levels of 25(OH)D compared to the other two genotypes. In patients, the TT genotype of the rs2228570 variant showed higher levels of 25(OH)D compared to CC + TC in the same polymorphism. The frequency of each SNP alone was not significantly different between patients and controls. However, was observed a cumulative effect of minor alleles of SNPs at the DHCR7, GC, CYP2R1 and CYP24A1 loci on the susceptibility to type 1 diabetes.
Type 1 Diabetes	Thorsen SU, 2014 [58]	Denmark	Cohort Study	1467 trios	NA	TaqMan Genotyping Assay	No	VDR, CYP27B1, CYP24A1, CYP2R1, DHCR7 and GC	BsmI (rs1544410), FokI (rs2228570), ApaI (rs7975232), CYP27B1 (rs4646536), GC (rs2282679), CYP2R1 (rs10741657),	The hypothesis that a different distribution of SNPs from vitamin D metabolism genes is associated with T1D was not confirmed by study. Though an association between genetic variation in the GC

(continued on next page)

Table 1 (continued)

Autoimmune disease	Author; Year	Country	Study Design	N Case/Controls	Mean Age of Cases/ Controls (Year)	Methodology of variants identification	Adjusted Factors	Gene	Studied Variants	Relevant Key Findings
Type 1 Diabetes	Tapia G, 2019 [59]	Norway	Case-Control	189/576	12,7/11,7	Custom Golden Gate Assay	Child's HLA genotype, sex, cesarean delivery, maternal ethnicity, prepregnancy BMI, smoking in pregnancy, and age at delivery	VDR, CYP2R1, CYP24A1, CYP27B1, GC and DHCR7	DHCR7 (rs12785878), and CYP24A1 (rs6013897) GC (rs2282679), DHCR7 (rs12785878, CYP2R1 (rs10741657), CYP24A1 (rs6013897), CYP27B1 (rsrs703842), and VDR (rs1544410 and rs11568820)	locus and 25(OH) D levels was confirmed. Higher maternal DBP level at delivery may decrease offspring T1D risk. Increased 25(OH) D levels at birth may decrease T1D risk, depending on VDR genotype.
Type 1 diabetes	Rasoul MA, 2019 [60]	Kuwait	Case-Control	253/214	8,5/8,9	PCR-RFLP	No	VDR	FokI, (rs10735810), BsmI, (rs1544410), TaqI, (rs731236) and ApaI (rs7975232)	The findings reported in this study show that the VDR gene FokI and TaqI polymorphisms are associated with susceptibility to T1DM in Kuwaiti Arabs. The VDR polymorphisms ApaI and BsmI did not show a positive association with T1DM
Diabetes Mellitus	Vedralová, M., 2012 [61]	Czech Republic	Case-Control	54 DM1 without nephropathy, 116 DM2 without nephropathy, 132 diabetic patients nephropathy, 47 diabetic patients with nondiabetic renal disease/ 118	NA	PCR-RFLP	No	VDR	TaqI (rs731236), BsmI (rs1544410), ApaI (rs7975232) and FokI (rs2228570)	The BsmI, ApaI and TaqI polymorphisms had no difference in frequency of expression. The F allele of the FokI polymorphism presented a higher risk of diabetic nephropathy and the distribution of alleles of this polymorphism was significant, since F

(continued on next page)

Table 1 (continued)

Autoimmune disease	Author; Year	Country	Study Design	N Case/Controls	Mean Age of Cases/ Controls (Year)	Methodology of variants identification	Adjusted Factors	Gene	Studied Variants	Relevant Key Findings
										was more present in patients with nephropathy than f. Analyzing the combination of VDR polymorphisms, it was found that BBFFAATt was the most common allelic combination in individuals with diabetic nephropathy and absent in control individuals, and BbFFAaTt was more frequent in individuals with T2D.
Diabetes Autoimmune study in the Young	Frederiksen, B., 2013 [218]	United States of America	Case-Control	111/1570	NA	Illumina 48-plex (VeraCode), PCR-based linear array genotyping Assay and TaqMan Genotyping Assay	Age, risk of Islet Autoimmunity and progression to type 1 diabetes, self-reported ethnicity, first positive autoantibody	VDR and PTPN2	BsmI (rs1544410), FokI (rs2228570), Cdx2 (rs11568820) and PTPN2 (rs1893217 and rs478582)	There was no relationship between the development of islet autoimmunity (IA) and any variant evaluated. The progression to the development of type 1 diabetes in children with IA was related to rs2228570 GG. The rs1544410 (VDR) 'AA/AG' and rs1893217 (PTPN2) 'AA' decreasing the risk of T1D. The interaction rs1893217 (PTPN2) 'GG/GA' with the rs1544410 (VDR) variant 'AA/AG' was not associated with T1D

(continued on next page)

Table 1 (continued)

Autoimmune disease	Author; Year	Country	Study Design	N Case/Controls	Mean Age of Cases/ Controls (Year)	Methodology of variants identification	Adjusted Factors	Gene	Studied Variants	Relevant Key Findings
Diabetic nephropathy	Martin, R., 2010 [219]	United Kingdom	Case-Control	655 nephropaths/ 674 non-nephropaths	NA	Pyrosequencing, TaqMan Genotyping Assay, Sequenom or direct sequencing technologies	Population stratification	VDR, CYP27B1 and CYP2R1	VDR: rs4303288, rs11168275, rs12721366, rs2544043, FokI (rs10735810), BsmI (rs1544410), ApaI (rs7975232) and TaqI (rs731236); CYP27B1 (rs4646536), and CYP2R1 (rs10741657). TaqI (rs731236)	The rare AGT haplotype (BsmI/ ApaI/TaqI) demonstrated protection against nephropaty (3.1% cases versus 5.8% controls).
Diabetic Retinopathy	Taverna, MJ., 2002[62]	France	Case-Control	101/99	NA	PCR-RFLP	Age, sex, diabetes duration and clinical data	VDR	TaqI (rs731236)	The wild-type TT' genotype was less present in the case group, therefore it represents a low risk of developing severe retinopathy. The 'tt' frequency showed no differences. The 'Tt' frequency, is associated with the risk of severe retinopathy in patients with glycated hemoglobin >9.0%. The TT genotype was lower frequent in patients with more than 25 years of disease.
Addison's disease	Pani, MA., 2002[63]	Germany	Case-Control	95/220	NA	PCR-RFLP	No	VDR	FokI (rs10735810), BsmI (rs1544410), TaqI (rs731236) and	Significant differences were observed for ff, tt and bb genotype between patients and controls, but no significant

(continued on next page)

Table 1 (continued)

Autoimmune disease	Author; Year	Country	Study Design	N Case/Controls	Mean Age of Cases/ Controls (Year)	Methodology of variants identification	Adjusted Factors	Gene	Studied Variants	Relevant Key Findings
Addison's disease	Fichna, M., 2009 [222]	Poland	Case-Control	101/251	35,8/59,4	PCR-RFLP	No	CYP27B1	Apal (rs7975232) rs10877012	differences were observed for the Apal polymorphism. There was a prevalence of the C (rs10877012) allele in patients with AAD than in the control group, as well as the frequency of the 'CC' genotype, tending to be 2-fold as likely to develop AAD than other genotypes.
Alopecia Areata	Ates, O., 2017 [223]	Turkey	Case-Control	198/167	32.62 ± 9.621/31.56 ± 11.319	PCR-RFLP	No	VDR	BsmI (rs1544410); Apal (rs7975232) and TaqI (rs731236)	No association was found between the genetic variants studied and the genetics of Alopecia Areata
Autoimmune Connective Tissue: systemic lupus erythematosus, primary Sjogren's syndrome, and with rheumatoid arthritis	Latini A, 2021 [64]	Italy	Case-Control	SLE 308, pSS 195, RA 92/246	NA	TaqMan Genotyping Assay	No	VDR	rs2228570, rs7975232 and rs731236	For rs7975232 SNP, it was observed a significant association of the variant homozygous genotype with SLE, pSS, and RA susceptibility. Moreover, it reported associations of this genotype with clinical phenotypes of SLE and pSS. Lastly, the GG genotype of rs731236 was associated with a lower RA susceptibility
Axial Spondyloarthritis	Bugaj B, 2022 [65]	Poland	Case-Control	106/122	42,7 (±12.9)/ NA	PCR-RFLP	No	VDR	FokI (rs2228570),	No associations were identified

(continued on next page)

Table 1 (continued)

Autoimmune disease	Author; Year	Country	Study Design	N Case/Controls	Mean Age of Cases/ Controls (Year)	Methodology of variants identification	Adjusted Factors	Gene	Studied Variants	Relevant Key Findings
									<i>BsmI</i> (rs1544410), <i>Apal</i> (rs7975232) and <i>TaqI</i> (rs731236)	between any of the studied polymorphisms and disease susceptibility. The study found higher prevalence for the rs731236 CT genotype among female patients compared to males.
Celiac disease	Marild, K., 2017 [66]	Norway	Case-Control	416/570	NA	Custom GoldenGate Assay	No	66 tagSNPs	CYP2R1 (rs10741657), CYP24A1 (rs6013897), GC (rs2282679), and DHCR7 (rs12785878)	Maternal and child vitamin D genetic variants did not predict the risk of celiac disease in the offspring. In addition, no association was found in the genetic variants studied and later celiac disease
Celiac disease and Type 1 Diabetes	San-Pedro, JI., 2005 [67]	Spain	Case-Control	39/88 and 71/88	NA	PCR-RFLP	No	VDR	<i>FokI</i> (rs2228570), <i>BsmI</i> (rs1544410), <i>Apal</i> (rs7975232) and <i>TaqI</i> (rs731236)	The VDR ‘ff’ genotype was associated with celiac disease. In diabetes there was no such association, but the ‘fABt’ haplotype was reported. The polymorphisms studied are markers of predisposition or protection to autoimmunity.
Graves’ Disease	Ramos-Lopes, E., 2005 [228]	Germany, Polish and Serbian	Case-Control	789/823	NA	PCR-RFLP	Number of different alleles or haplotypes tested	VDR	<i>Apal</i> (rs7975232), <i>TaqI</i> (rs731236), <i>BsmI</i> (rs1544410)	The <i>Apal</i> and <i>TaqI</i> SNPs had no distribution difference. The <i>BsmI</i> polymorphism was associated with

(continued on next page)

Table 1 (continued)

Autoimmune disease	Author; Year	Country	Study Design	N Case/Controls	Mean Age of Cases/Controls (Year)	Methodology of variants identification	Adjusted Factors	Gene	Studied Variants	Relevant Key Findings
Graves' Disease and Hashimoto's Thyroiditis	Pani, MA., 2002[68]	Germany and Italy	Cohort Study	561 individuals (187 families – 95 of GD and 92 of HT)	NA	PCR, PCR-RFLP and nested PCR	No	GC	and <i>FokI</i> (rs2228570) GC intron 8 (TAAA)N repeat (alleles 6 (187 bp), 8 (195 bp), 10 (203 bp), 11 (207 bp), D416E (rs7041) and T420K (rs4588)	Graves' disease in the Polish population, associated with the greater presence of 'bb' in the case groups of this ethnicity. The <i>FokI</i> variant f was associated in both German and Polish patients. In general, these polymorphisms were not associated with Serbs. GC intron 8 (TAAA)N repeat polymorphism was associated with Graves' disease but not with Hashimoto's thyroiditis. In both conditions, no significant association was observed neither GC D416E nor DBP T420K. Furthermore, no significant interaction between GC genotypes and <i>HLA-DQ2</i> haplotype was observed
Hashimoto's thyroiditis	Djurovic, J., 2015 [69]	Serbia	Case-Control	44/32	NA	PCR-RFLP	Age, sex and geographically	VDR	<i>FokI</i> (rs2228570), <i>Apal</i> (rs7975232) and <i>TaqI</i> (rs731236)	The analysis indicates a significant difference in the genotype distribution of the <i>FokI</i> polymorphism (continued on next page)

Table 1 (continued)

Autoimmune disease	Author; Year	Country	Study Design	N Case/Controls	Mean Age of Cases/ Controls (Year)	Methodology of variants identification	Adjusted Factors	Gene	Studied Variants	Relevant Key Findings
Hashimoto's thyroiditis	Hanna H, 2021 [70]	Egypt	Case-Control	112 patients with Hashimoto's thyroiditis and 48 hypothyroid non-HT subjects	40/45	TaqMan SNP Genotyping Assay	No	VDR	<i>FokI</i> (rs2228570) and <i>BsmI</i> (rs1544410)	between patients and the control group, suggesting that Serbian women with 'FF' are at greater risk of developing the disease. Regarding the <i>Apal</i> and <i>TaqI</i> polymorphisms, there was a higher frequency of the variant allele, but there was no significant difference between the case and control groups. <i>FokI</i> AA genotype is more frequent in HT patients compared to hypothyroid non-HT subjects. Patients with <i>FokI</i> AA genotype have statistically higher levels of 25–OH-vitamin D3.
Immune Thrombocytopenic Purpura	Yesil S, 2017 [71]	Turkey	Case-Control	44/100	NA	ABI PRISM SNaPshot® Multiplex mini-sequencing	No	VDR	<i>Cdx-2</i> (rs11568820), <i>FokI</i> (rs2228570), <i>BsmI</i> (rs1544410), <i>Apal</i> (rs11168271), and <i>TaqI</i> (rs731236)	The homozygote GG genotype of <i>Cdx-2</i> was more frequent in patients and the A allele of was associated with a decreased risk of disease in children.
Inflammatory Bowel disease	Eloranta, JJ., 2011 [233]	Switzerland	Case-Control	636/248	42.5 ± 5.1/ 44.2 ± 17.0	TaqMan Genotyping Assay	Sex and age	GC	D416E (rs7041) and T420K (rs4588)	The GC 416 Glu variant had no significant association with IBD, however it showed a tendency for this variant to be more common

(continued on next page)

Table 1 (continued)

Autoimmune disease	Author; Year	Country	Study Design	N Case/Controls	Mean Age of Cases/ Controls (Year)	Methodology of variants identification	Adjusted Factors	Gene	Studied Variants	Relevant Key Findings
Juvenile idiopathic arthritis	Marini F, 2020 [72]	Italy	Cohort Study	103	20.21 ± 7.11	Sanger sequencing	No	VDR	<i>ApaI</i> (rs797532), <i>BsmI</i> (rs1544410) <i>TaqI</i> (rs731236) <i>Cdx2</i> (rs11568820), <i>FokI</i> (rs2228570)	in the case group than in controls, indicating pathogenesis in its presence. The 420 Lys variant was more common in controls, it can be considered that it has a protective role Vitamin D status resulted to be independent of <i>VDR</i> genotypes. <i>ApaI</i> genotypes showed a highly significant different distribution between JIA patients and unaffected controls, with both the TT genotype and the T allele significantly more frequent in patient group
Rheumatoid arthritis	Maalej, A., 2005 [73]	France	Cohort Study	2 groups of 100 trios affected with one RA patient and both parents.	NA	PCR-RFLP	No	VDR	<i>FokI</i> (rs10735810), <i>BsmI</i> (rs1544410) and <i>TaqI</i> (rs731236)	The analysis shows a difference between the transmissibility of the F allele of <i>FokI</i> , with the 'F/F' genotype being more frequent in RA patients. <i>BsmI</i> and <i>TaqI</i> showed no difference in distribution
Rheumatoid arthritis	Yoshida, S., 2014 [74]	Japan	Cohort Study	1957 patients	NA	TaqMan Genotyping Assay	Age, gender, disability score, biochemistry parameters and treatment	<i>GC</i> , <i>DHCR7</i> / <i>NADSYN1</i> and <i>CYP2R1</i>	<i>GC</i> (rs2282679), <i>DHCR7</i> / <i>NADSYN1</i> (rs3829251, rs12785878)	The minor <i>GC</i> allele was strongly associated with patients with low serum concentrations of

(continued on next page)

Table 1 (continued)

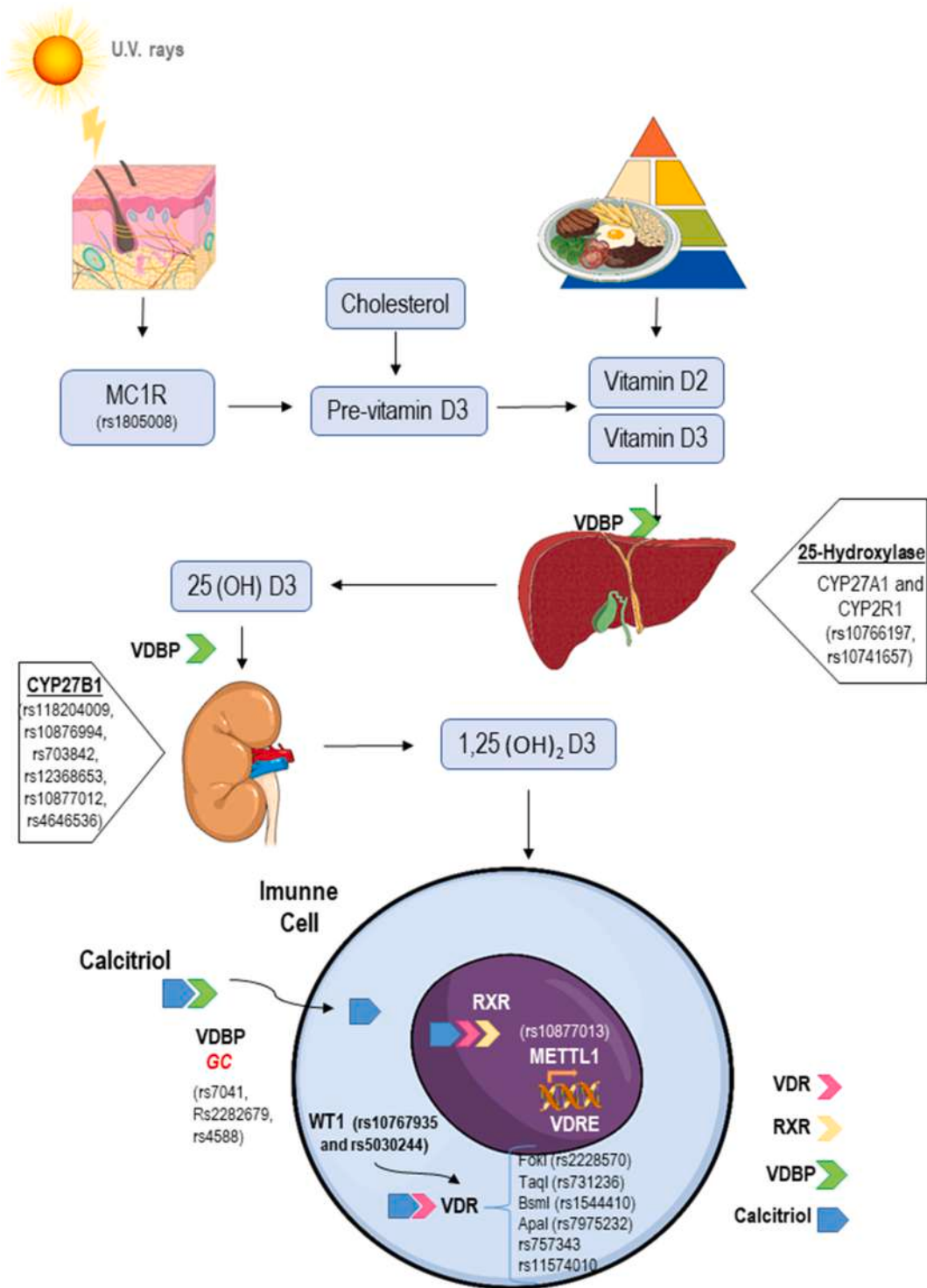
Autoimmune disease	Author; Year	Country	Study Design	N Case/Controls	Mean Age of Cases/ Controls (Year)	Methodology of variants identification	Adjusted Factors	Gene	Studied Variants	Relevant Key Findings
Rheumatoid arthritis	Despotovic, 2021 [75]	Republic of Serbia	Case-Control	143/105	57,04 ± 12.48/56 ± 16.59	PCR-RFLP	No	VDR	and rs1790349) and CYP2R1 (rs10741657) FokI (rs2228570), BsmI (rs1544410), ApaI (rs7975232), and TaqI (rs731236)	25(OH)D3 and could be a risk factor for hip fracture in Japanese RA patients The results indicate an association of f allele carriers (FokI) and increased susceptibility to RA, as well as with all the different outcomes. Haplotype analysis showed difference in the distribution of BsmI/ApaI (Ba) haplotype carriers in RA with associated osteopenia compared to controls
Rheumatoid Arthritis	Brink, M, 2018 [76]	Sweden	Case-Control	515/267	54,5 ± 9.4/ 53,9 ± 9.3	TaqMan Genotyping Assay	BMI, sampling time of year (dark/light), smoking ever, educational level (academic/no academic), age at the time of sampling	GC	GC (rs4588 and rs7041)	The genotype, allele frequencies or haplotype combinations not differ between cases and controls. However, was observed a significant relationship between increase levels of DBP when adjusting for 25 (OH) D levels and the minor allele (A) of SNP rs4588 and BMI (p < 0.05) in females.
Rheumatoid Arthritis	Punceviciene E, 2021 [239]	Lithuania	Case-Control	206/180	55,01 ± 11.08/53,15 ± 10.68	TaqMan Genotyping Assay	No	VDR	TaqI (rs731236), BsmI	Genotypic and allelic frequency distributions four (continued on next page)

Table 1 (continued)

Autoimmune disease	Author; Year	Country	Study Design	N Case/Controls	Mean Age of Cases/ Controls (Year)	Methodology of variants identification	Adjusted Factors	Gene	Studied Variants	Relevant Key Findings
									(rs1544410), <i>Apal</i> (rs7975232), and <i>FokI</i> (rs2228570)	<i>VDR</i> loci tested does not differ between the group of RA patients and controls. However, Vitamin D concentration in RA patients and controls carrying major alleles of <i>TaqI</i> , <i>BsmI</i> , and <i>FokI</i> variants were significantly different in both groups, and all genotypes for <i>Apal</i> .
Rheumatoid Arthritis	Hussien YM, 2013[77]	Egypt	Case-Control	200/150	57,3/57,01	PCR-RFLP	No	<i>VDR</i>	<i>VDR</i> : <i>BsmI</i> (rs1544410)	It was found a significant association between lower hip (BMD-h) and genotype variants of <i>VDR (BsmI)</i> in RA patients with osteoporosis.
Vitiligo	Sobeih, S., 2016[78]	Egypt	Case-control	75/75	31.5 (13.5)/ No	PCR-RFLP	Age and Sex	<i>VDR</i>	<i>Apal</i> (rs7975232), <i>TaqI</i> (rs731236) and <i>FokI</i> (rs10735810)	The frequency of t <i>Apal</i> genotype (aa) and the variant genotype (tt) of <i>TaqI</i> were higher between the patients, may be a risk for the development of vitiligo in this population. But serum 25(OH)D levels were not significantly different among the different genotypes

Abbreviation: MS: Multiple Sclerosis; SLE: Systemic Lupus Erythematosus. T1D: Type 1 Diabetes; RA: Rheumatoid arthritis; AIT: Autoimmune Thyroid Disorder; pSS: Primary Sjogren’s Syndrome; HT: Hashimoto’s thyroiditis; ITP: Immune Thrombocytopenic Purpura; DAISY: Diabetes Autoimmune study in the Young; JIA: Juvenile idiopathic arthritis.

Table 1 details all studies included in this systematic review. We extracted important data from papers published between 2000 and 2022, conducted in different countries including Australia, Belgium, Brazil, China, Croatia, Czech Republic, Denmark, Egypt, Finland, France, Germany, Greece, India, Italy, Japan, Kingdom of Saudi Arabia, Kuwait, Lithuania, Mexico, Netherlands, Norway, Poland, Polish, Portugal, Serbia, Spain, Slovak Republic, Sweden, Switzerland, Turkey, United Kingdom (UK) and United States of America



(caption on next page)

Fig. 1. Main genetic variants found in genes related to Vitamin D signaling and autoimmune diseases. The skin produces around 80% of Vitamin D and the remaining 20% is obtained from the diet. Cholesterol molecules are metabolized into pre-vitamin D3 through the incidence of UV rays on MC1R receptors. In blood, Vitamin D binding protein to VDBP to be transported to the liver. In the liver, the CYP27A1 and CYP2R1 enzymes catalyze the action of 25-hydroxylase in the hydroxylation of vitamin D3 to 25(OH)D3. Once again, VDBP transport Vit D metabolites. In the kidneys, the CYP27B1 enzyme is able to hydroxylate 25(OH)D3 to 1,25(OH)2D3, the active form of Vitamin D. After Vitamin D active (calcitriol) enters target cells and binds to vitamin D receptor VDR. At cellular level, VDR-calcitriol complex in the cytosol is translocated to the nucleus, where it binds to RXR, which interacts with VDRE in vitamin D target genes. Some VDREs are located within *METTL1* gene. Furthermore, *VDR* gene is a downstream target of *WT1* and may be regulated its expression. MC1R: melanocortin-1 receptor; VDBP: vitamin D binding protein; VDR: vitamin D receptor; RXR: retinoid X receptor; VDRE: vitamin D response elements.

(USA). A full list of all identified papers is found in Supplementary Material. Among the papers incorporated into the analysis, 53 were case-control studies, 13 had a cohort design, 1 had a trio family dataset design, 1 had a familial study design and 1 had cross-sectional study design. It is important to highlight that some articles presented more than one type of study design. Most studies evaluate genetic variants of diseases such as Multiple Sclerosis, Systemic Lupus Erythematosus, Type 1 Diabetes, Addison's disease, and Rheumatoid arthritis. It is important to note that our protocol returned more studies with adult subjects (31) than children (03). The mean age for the adults patients was 38.44 (SD = 9.75) and for pediatric patients was 10.9 (SD = 2,16).

Appropriate genotyping methods were used in all included studies. Polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) was used by 32 studies as the genotyping method. Twenty-four studies used TaqMan Genotyping Assay and a couple of methodologies of sequencing. It is also relevant to note that some papers presented more than one type of methodology.

Some statistical strategies were used to control possible confounding factors, which included adjust for age, gender, genotype, country/region origin, risk of disease progression, first positive autoantibody, number of different alleles or haplotypes tested, month of sample collection, disease duration, population stratification, ethnicity, sun exposure, smoking history, vitamin D levels and other clinical data (see Table 1). In total, 87 genetic variants, including in *VDR*, *GC*, *PTPN2*, *CYP27B1*, *CYP2R1*, *CYP24A1*, *CYP27A1*, *METTL1*, *WT1*, *PTPN22*, *PDCD1*, *NADSYN1/DHCR7*, *RXR*, *MC1R*, *KLOTHO*, *FOXP3* and *GATA3* genes were identified. Fifty-nine studies suggested that different genetic variants in Vit D signaling genes can be associated with autoimmune diseases susceptibility and several outcomes. However, the authors Irizar et al., Agnello et al., García-Martin et al., Barizzzone et al., Scazzzone et al., didn't identify an association between the genetic variants and Multiple Sclerosis. Also, Ates et al. did not find any association with Alopecia Areata [79–85].

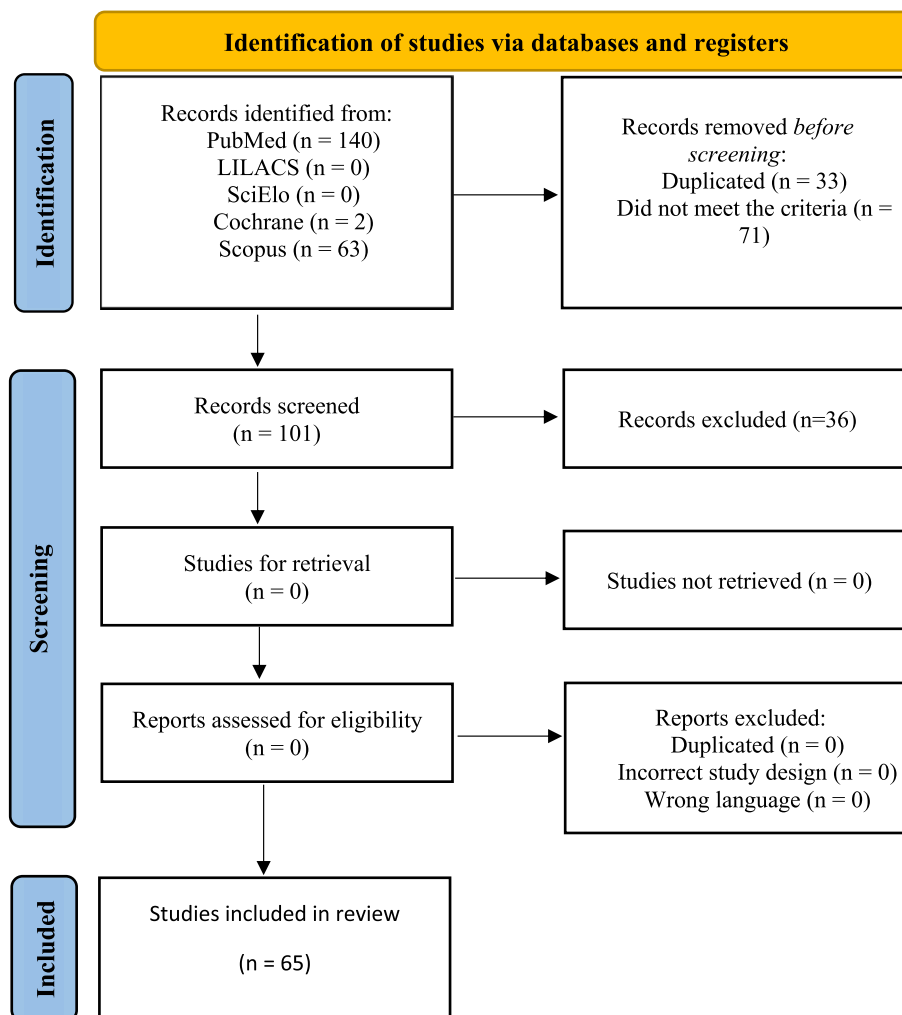
4. Discussion

In face of a plethora of functions of Vit D and increasing knowledge about the genes that it regulates (over 200), currently, its notable aspects revolve around the potential therapeutic applications and preventive influence of this vitamin in numerous diseases [86–88]. Saternus et al. present genetic evidence that variants of 11 from 29 investigated genes (960 SNPs) are related in skin pigmentation and are predictive serum levels of 25(OH)D [31]. In this sense, genetic association studies had reported variants that might affect the structure and/or function of different proteins important for Vit D signaling and, consequently, the susceptibility to several autoimmune diseases is increased [89]. Nevertheless, certain observations frequently exhibit inconsistencies across diverse global populations, and fail to explain whether genetic variant is associated of loss or gain-of-function.

Lifestyle factors, encompassing exposure to sunlight, dietary supplementation and intake, as well as climatic conditions and geographical latitude, play a pivotal role in determining Vit D status [90,91]. Ethnicity is thought to significantly influence Vitamin D synthesis, which can be related to melanin pigmentation and possibly metabolism [92,93]. In the last decade, GWAS have demonstrated an increasing number of genetic variants that affect synthesis, metabolism and transport of vitamin D. These variants display specific frequencies in certain populations [94]. In a large-scale GWAS meta-analysis involving 31 studies with 79,366 participants of European ancestry and replication in 40,562 samples, four significant loci were identified (rs3755967 in *GC*, rs12785878 in *NADSYN1/DHCR7*, rs10741657 in *CYP2R1*, rs1721670 in *CYP24A1*) [95]. This study recapitulated the findings of a previous study by Wang et al. and discovered two additional variants (rs8018720 in *SEC23A* and rs10745742 in *AMDHD1*) involved in the genetic makeup associated with 25-hydroxyvitamin D levels [96]. So far, few studies have addressed the cellular and molecular mechanism of genetic variants related with Vit D and their impact on the immune system. This makes it difficult to understand the functional impact of these observational studies.

Indeed, variants in the *VDR* gene are the most widely studied and approximately 500 SNPs have already been identified [97]. Among the publications included in our review, the most intensively studied *VDR* polymorphisms are *FokI* (rs2228570), *TaqI* (rs731236), *BsmI* (rs1544410), and *ApaI* (rs7975232) variants. For note, these SNPs are in strong linkage disequilibrium (LD). *FokI* results in an alternative initiation codon (ATG) codon, *BsmI* and *ApaI* are located in the 3' region of the gene, while *TaqI* is a synonymous variant. While these four SNPs do not induce alterations in the amino acid sequence of the protein, they have the potential to impact mRNA stability and gene transcription [33]. Few papers have found the influence of intronic rs757343 SNP, known as *Tru9I*, with on the susceptibility or outcome of an autoimmune disease. Although not yet known if rs757343 have any functional effect, in a case-parent trio study with population of South Croatia observed a possible protective role of the *Tru9I* minor allele in T1D etiology [98]. Another variant identified in the *VDR* gene, which is still little studied, is rs17878969, a variant of the DELINS type at the 3' untranslated region and most associated in the literature with susceptibility to infectious diseases [99,100].

The presence of the variant in *FokI* defined as f (ATG codon) translate the protein in complete form (427 amino acids), while the *FokI* variant defined as F (ACG codon) produces a slightly truncated protein (424 amino acids). Functional differences among



Flowchart 1. PRISMA flow diagram.

genotypes show that carriers of F code for a more active protein that interacts more efficiently with transcription factors and exhibits greater transcriptional activity when compared with full-length VDR protein [101,102]. In a study by van Etten et al., it was demonstrated that human lymphocytes with wild type *FokI* genotype (short FF VDR) proliferated more actively, and monocytes and dendritic produced higher levels of IL-12 [103]. Likewise, in a Japanese studied was observed that T1D patients who were carriers of the *BsmI* BB genotype produced higher levels of IFN γ than in the Bb and bb genotype groups ($p < 0.05$) [104]. Effectively, the role of genetic variants in the *VDR* gene may vary depending on the autoimmune disease studied, ethnicity and sun exposure. Alternatively, each variant might only impart a modest level of risk. As shown in Table 1, the *Apa1* variant has shown the least association with risk factors for autoimmune diseases or vitamin D deficiency.

Taking ethnicity into account, it has been observed that Chinese, Portuguese and Egyptian patients exhibit significantly higher frequencies of the *BsmI* B allele in SLE compared to control patients. Meanwhile, Abbasi et al. did not find the same result in subjects living in northeastern Iran [105–109]. Another study showed that variants in *BsmI* and *FokI* were not found to be risk factors for SLE in a Brazilian-European cohort [110]. Interestingly, Martin et al., 2010 showed a protective role of rare AGT haplotype in *VDR* gene (rs1544410, rs7975232 and rs731236) against diabetic nephropathy in patients with T1D from UK and Ireland patients [111]. Therefore, there is a clear indication that ethnicity significantly contributes to the variation in the discrepancy in *VDR*'s variants, not only in multiple sclerosis but also in other autoimmune diseases. Other co-segregating genetic factors, such as the *HLA-DRB1*15* positive haplotype, may also contribute to these differences [33,112,113].

Over recent years, research findings have highlighted connections between Vit D status and skin pigmentation [114]. Especially in the context of autoimmune diseases, MS is the main disease studied in relation to link between sun exposure and Vit D [115]. In this context, Dickinson et al. showed a significant interplay with sun exposure during childhood, 'G' allele of rs11574010 (*Cdx-2*) and MS risk [116]. The *Cdx-2* SNP is situated upstream at –3731 base pairs in 5'UTR of the *VDR* gene, is marked by an A to G substitution. This SNP does not exhibit LD with either the 3'UTR cluster or the *FokI* variants. However, it has been documented to be in LD with other

polymorphisms identified within the 5'UTR region [117].

Here, it is also necessary to highlight the importance of melanocortin 1 receptor (encoded by the gene *MC1R*) of melanocytes, which plays a pivotal role in the control of human skin pigmentation [118,119]. Previously, Asp294His variant in *MC1R* gene has been associated with MS risk in Northern European Caucasian patients, while the variant Arg160Trp was associated in Australia population [120,121]. The majority of variants described in this gene are related to a reduction of *MC1R* function [122,123]. The scientific community has debated the paradox of higher Vit D deficiency among darker-skinned individuals despite a lower incidence of MS in this group. Some authors propose that individuals with *MC1R* variants might be more vulnerable to the inflammatory effects induced by ultraviolet radiation (UVR), offering a potential explanation for this phenomenon [124–126].

Currently, some studies have also shown the epistasis amongst *PTPN2* and genes associated with the Vit D pathway [127]. Ramagopalan et al. using a ChIP-seq approach demonstrated that *VDR* has an intronic binding site in the *PTPN2* gene. These findings, together with some genetic association studies, may support the role of *PTPN2* on autoimmune diseases [128–130]. *PTPN2* exhibits ubiquitous expression and serves as a signaling molecule that regulates various cellular processes, encompassing cell growth, differentiation, mitotic cycle, oncogenic transformation and regulating inflammatory signaling [131–134]. It's important to acknowledge that certain studies propose modest associations between SNPs in *PTPN2* gene and autoimmune diseases. However, in combination with variants in the *PTPN22* have been shown to possibly increase the susceptibility of T1D, CD, and RA [135–137].

Another protein found in our searches was the Vitamin D-binding protein (DBP, encoded by *GC* gene), which is synthesized predominantly in liver parenchymal cells [138]. DBP mediates the main systemic transporter of ergocalciferol/cholecalciferol, calcitriol and calcitriol to target cells and tissues, as well as playing an important role in macrophage activation [139]. The serum concentrations of calcitriol have also been correlated with those DBP levels [140]. The main genetic polymorphisms already identified in *GC* gene are the variable (TAAA)_n repeat situated in intron 8 and in exon 11. These variants lead to amino acid change of aspartic acid for glutamic acid in codon 432 (rs7041) and threonine for lysine in codon 436 (rs4588) respectively. The functional impact is differences in the affinity for calcitriol and consequently low circulating levels of vit D metabolites in different populations [141–143].

Knowing that Vit D deficiency it is also common in Inflammatory bowel disease (IBD), Eloranta et al. identified that SNP rs4588 variant Lys is less frequent in IBD cases than in the healthy population and can be considered a protective variant [144–146]. On the other hand, in Polish population the variant *GC* rs4588 Lys has been associated with Graves' disease [147]. These controversial results difficult to understand the roles of DBP variants, but is important to note that the etiologies of IBD and Graves' disease are different.

Regarding the polymorphism rs7041 in *GC* gene, an interesting study showed that Asp/Glu and Glu/Glu variants are more frequent in subjects with type 1 diabetes and detectable tyrosine phosphatase-like insulinoma associated protein-2 (IA-2) autoantibodies, but the genotypes did not influence the prevalence of 65-kDa isoform of glutamic acid decarboxylase (GAD65) antibodies detection [148]. In addition, a GWAS study with European American ancestry individuals showed that individuals carrying the C allele for SNP rs2282679, were associated with lower serum calcitriol levels [149].

Numerous lines of evidence support an important role of genetic variants involved in Vit D metabolism, including in genes encoding the CYP450 enzymes [150]. The pre-vitamin D3 is metabolized to form 25(OH)D by enzymes CYP2R1 and CYP27A1 in the liver and then converted to its active form in the kidneys by CYP27B1 [114]. Previous studies showed that the SNP in *CYP2R1* (rs2060793) promotes the substitution of Pro → Leu at amino acid 99 in the protein (rs2060793), decreases the 25(OH)D3 levels and eliminates the enzymatic activity of vitamin D 25-hydroxylase [151]. Interestingly, in a study using bioinformatics tools and previously published data, Yarwood et al. observed that the four genetic variants in the *CYP2R1* gene associated with Vit D levels in rheumatoid arthritis are in intronic region [152]. In this systematic review, we identified different variants in *CYP2R1* gene related to Multiple Sclerosis, Type 1 Diabetes and Vogt-Koyanagi-Harada [153–156]. Both SNPs rs10741657 and rs10766197 have been significantly associated with lower Vit D concentrations in some autoimmune diseases [153,154,157]. Numerous hypotheses have been proposed to elucidate the sex-related variations in Vit D levels. One extensively studied hypothesis is associated with individuals harboring the AA genotype of the rs10766197 SNP exhibiting lower Vitamin D levels compared to those with the GG genotype, following adjustments for gender [158].

Notably, some studies that found evidence for an association between common variants in *CYP2R1* gene and T1D risk used a relatively small sample size, however, this association could not be substantiated in extensive genetic databases. For example, larger studies using the European population failed to uncover any evidence supporting an association between any *CYP2R1* variants and T1D [155,159]. The interpretation of these different results must take into consideration not only the sample size, but also the need for a more carefully designed, such as matched case-control studies that account for age, gender, ethnic groups and different outcomes.

Variants in the *CYP27B1* have previously been linked with MS, T1D and other autoimmune disease susceptibility, mainly in the Caucasian population [160–164]. In a mouse model of Vitamin D-dependent rickets type 1 (VDDR type 1), reduced levels of 1,25-dihydroxyvitamin D were observed in *Cyp27b1* homozygous knockout mice [165]. In human studies, the rs118204009 SNP induces a substitution from arginine to histidine change at position 389 of the protein (R389H), resulting in the functional impairment of CYP27B1 and reduction in the levels of activated Vit D [166,167]. Interestingly, this variant has not been identified in Han Chinese population with both MS and neuromyelitis optica disease [162]. Furthermore, the rs10877012 (–1260C > A) variant, situated in the promoter region, alters the putative binding site for the CDX2 transcription factor. The active Vit D and *CYP27B1* expression are affected by this SNP [160,168,169].

In the context of longevity, Vit D assumes a crucial role in mineral metabolism, cell proliferation and modulation of the immune response [15]. Considering the significance of Vit D in aging and its potential to reduce susceptibility to chronic degeneration in the elderly, a notable study was conducted in Spain examined 104 individuals in their eighties (85 years) and 114 controls within the age range of 17–40 years. The study observed an link between long life and the *VDR* 3'UTR GS (rs1544410-G:rs17878969-S) and five-marker GGCGS (rs11568820-G:rs4516035-G:rs10735810-C:rs15444 10-G:rs17878969-S) haplotypes in males reaching their

eighties, while such an association was not observed in females [170,171].

Lastly, it's noteworthy to emphasize that the presence of genetic variants in these genes may modify the response to Vit D supplementation, even in individuals without any reported disease. Khayyatadeh et al. identified that in healthy Iranian adolescents, those with the AA genotype for *CYP2R1* (rs10741657) SNP exhibited a 2.5-fold increase in calcidiol serum levels compared to individuals with the GG genotype after receiving for 9 weeks Vit D supplementation [172]. Similarly, Bahrami et al. reported that female health adolescents carrying the major AA genotype for rs10766197 in *CYP2R1* gene had higher Vit D concentrations after supplementation [173]. These findings also extend to studies with the adult population. A recent study with healthy adults showed that *DBP* rs4588 minor allele (TT), *CYP2R1* rs10766197 minor allele (AA) and rs12794714 minor allele (AA) were associated with lower response to vit D supplementation [174].

Our study also has some limitations that need to be considered. Given that autoimmune diseases share common molecular mechanisms, we performed only a descriptive analysis based on existing literature and as we found results for different diseases, it was not possible to perform a more robust statistical analysis such meta-analyses strategies [34,175]. Additionally, the studies included in our analysis varied in sample size, ethnicities and methodologies for identifying genetic variants, which may have contributed to conflicting results. Another limitation is the lack of information on dietary factors for all study participants, which could potentially have contributed to some conflicting results. Even if most of the analyzed SNPs are located in noncoding regions, it is worth noting that these variants explain 8-fold more heritability than protein coding variants in complex traits such as autoimmune diseases [176].

5. Conclusion

Fig. 1 summarizes the main genetic variants discussed here, which contribute to our understanding of Vit D effect on pathogenesis of autoimmune diseases. In fact, future larger studies with populations of well-defined ethnicities, dietary information, and to explore the role of variants and gene–gene interactions in heritability are necessary to achieve a more thorough comprehension of the genetic background and its relationship to serum Vit D concentration. In this context, we conclude that, considering the association between Vit D deficiency, dysregulation of the immune system, and the development of autoimmune diseases, the identification of genetic variants that can predict change in Vit D signaling could have a significant impact on improving the management and ongoing care of individuals with these conditions.

Data availability statement

No data were used for the study described in this article.

CRediT authorship contribution statement

Luisa Menezes Trefilio: Data curation, Formal analysis, Methodology, Writing – original draft. **Letícia Bottino:** Data curation, Formal analysis, Methodology, Writing – original draft. **Rafaella de Carvalho Cardoso:** Validation, Writing – review & editing. **Guilherme Carneiro Montes:** Validation, Writing – review & editing. **Fabírcia Lima Fontes-Dantas:** Conceptualization, Funding acquisition, Methodology, Supervision, Validation, Writing – original draft.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors thank PhD Gildacio Pereira Chaves Filho for thoughtful discussions and critical reading of the manuscript. This work was supported by the Fundação de Amparo à Pesquisa do Estado do Rio de Janeiro (FAPERJ) to F.L.F.-D (SEI-260003/002985/2024) and L.M.T (SEI-260003/001342/2024). Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) to R.C.C (88887.892473/2023-00).

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.heliyon.2024.e27700>.

References

- [1] M.F. Holick, Vitamin D deficiency, *N. Engl. J. Med.* 357 (2007) 266–281, <https://doi.org/10.1056/NEJMra070553>.
- [2] M.E. Holthrop, K.A. Cox, D.L. Carnes, M.F. Holick, Effects of serum calcium and phosphorus on skeletal mineralization in vitamin D-deficient rats, *Am. J. Physiol. Metab.* 251 (1986) E234–E240, <https://doi.org/10.1152/ajpendo.1986.251.2.E234>.

- [3] M. Olliver, L. Spelmink, J. Hiew, U. Meyer-Hoffert, B. Henriques-Normark, P. Bergman, Immunomodulatory effects of vitamin D on innate and adaptive immune responses to *Streptococcus pneumoniae*, *J. Infect. Dis.* 208 (2013) 1474–1481, <https://doi.org/10.1093/infdis/jit355>.
- [4] K. Yin, D.K. Agrawal, Vitamin D and inflammatory diseases, *J. Inflamm. Res.* 7 (2014) 69–87, <https://doi.org/10.2147/JIR.S63898>.
- [5] D. Tiosano, G. Wildbaum, W. Gepstein, O. Verbitsky, Y. Weisman, N. Karin, A. Ezioni, The role of vitamin D receptor in innate and adaptive immunity: a study in hereditary vitamin D-resistant rickets patients, *J. Clin. Endocrinol. Metab.* 98 (2013) 1685–1693, <https://doi.org/10.1210/jc.2012-3858>.
- [6] E. Benedik, Sources of vitamin D for humans, *Int. J. Vitam. Nutr. Res.* 92 (2022) 118–125, <https://doi.org/10.1024/0300-9831/a000733>.
- [7] V.F. Logan, A.R. Gray, M.C. Peddie, M.J. Harper, L.A. Houghton, Long-term vitamin D3 supplementation is more effective than vitamin D2 in maintaining serum 25-hydroxyvitamin D status over the winter months, *Br. J. Nutr.* 109 (2013) 1082–1088, <https://doi.org/10.1017/S0007114512002851>.
- [8] L.A.G. Armas, B.W. Hollis, R.P. Heaney, Vitamin D2 is much less effective than vitamin D3 in humans, *J. Clin. Endocrinol. Metab.* 89 (2004) 5387–5391, <https://doi.org/10.1210/jc.2004-0360>.
- [9] C. Karohl, S. Su, M. Kumari, V. Tangpricha, E. Veledar, V. Vaccarino, P. Raggi, Heritability and seasonal variability of vitamin D concentrations in male twins, *Am. J. Clin. Nutr.* 92 (2010) 1393–1398, <https://doi.org/10.3945/ajcn.2010.30176>.
- [10] S.-M. Orton, A.P. Morris, B.M. Herrera, S. V Ramagopalan, M.R. Lincoln, M.J. Chao, R. Vieth, A.D. Sadovnick, G.C. Ebers, Evidence for genetic regulation of vitamin D status in twins with multiple sclerosis, *Am. J. Clin. Nutr.* 88 (2008) 441–447, <https://doi.org/10.1093/ajcn/88.2.441>.
- [11] U. Querfeld, Vitamin D and inflammation, *Pediatr. Nephrol.* 28 (2013) 605–610, <https://doi.org/10.1007/s00467-012-2377-4>.
- [12] S. V Ramagopalan, N.J. Maugeri, L. Handunnetthi, M.R. Lincoln, S.-M. Orton, D.A. Dymant, G.C. DeLuca, B.M. Herrera, M.J. Chao, A.D. Sadovnick, G.C. Ebers, J.C. Knight, Expression of the multiple sclerosis-associated MHC class II allele HLA-DRB1*1501 is regulated by vitamin D, *PLoS Genet.* 5 (2009) e1000369, <https://doi.org/10.1371/journal.pgen.1000369>.
- [13] E. Cocco, A. Meloni, M.R. Murru, D. Corongiu, S. Tranquilli, E. Fadda, R. Murru, L. Schirru, M.A. Secci, G. Costa, I. Asunis, S. Cuccu, G. Fenu, L. Lorefice, N. Carboni, G. Mura, M.C. Rosatelli, M.G. Marrosu, Vitamin D responsive elements within the HLA-DRB1 promoter region in Sardinian multiple sclerosis associated alleles, *PLoS One* 7 (2012) e41678, <https://doi.org/10.1371/journal.pone.0041678>.
- [14] L. Nagy, A. Szanto, I. Szatmari, L. Széles, Nuclear hormone receptors enable macrophages and dendritic cells to sense their lipid environment and shape their immune response, *Physiol. Rev.* 92 (2012) 739–789, <https://doi.org/10.1152/physrev.00004.2011>.
- [15] M. Hewison, Vitamin D and immune function: an overview, *Proc. Nutr. Soc.* 71 (2012) 50–61, <https://doi.org/10.1017/S0029665111001650>.
- [16] M.D. Griffin, W. Lutz, V.A. Phan, L.A. Bachman, D.J. McKean, R. Kumar, Dendritic cell modulation by 1 α ,25 dihydroxyvitamin D3 and its analogs: a vitamin D receptor-dependent pathway that promotes a persistent state of immaturity in vitro and in vivo, *Proc. Natl. Acad. Sci. U. S. A.* 98 (2001) 6800–6805, <https://doi.org/10.1073/pnas.121172198>.
- [17] L. Piemonti, P. Monti, M. Sironi, P. Fraticelli, B.E. Leone, E. Dal Cin, P. Allavena, V. Di Carlo, Vitamin D3 affects differentiation, maturation, and function of human monocyte-derived dendritic cells, *J. Immunol.* 164 (2000) 4443–4451, <https://doi.org/10.4049/jimmunol.164.9.4443>.
- [18] L.E. Jeffery, F. Burke, M. Mura, Y. Zheng, O.S. Qureshi, M. Hewison, L.S.K. Walker, D.A. Lammas, K. Raza, D.M. Sansom, 1,25-Dihydroxyvitamin D3 and IL-2 combine to inhibit T cell production of inflammatory cytokines and promote development of regulatory T cells expressing CTLA-4 and FoxP3, *J. Immunol.* 183 (2009) 5458–5467, <https://doi.org/10.4049/jimmunol.0803217>.
- [19] D.-H. Kim, C.A. Meza, H. Clarke, J.-S. Kim, R.C. Hickner, Vitamin D and Endothelial function, *Nutrients* 12 (2020) 575, <https://doi.org/10.3390/nu12020575>.
- [20] M.C. Gauzzi, C. Purificato, K. Donato, Y. Jin, L. Wang, K.C. Daniel, A.A. Maghazachi, F. Belardelli, L. Adorini, S. Gessani, Suppressive effect of 1 α ,25-dihydroxyvitamin D3 on type I IFN-mediated monocyte differentiation into dendritic cells: impairment of functional Activities and Chemotaxis, *J. Immunol.* 174 (2005) 270–276, <https://doi.org/10.4049/jimmunol.174.1.270>.
- [21] L.A. Lyakh, M. Sanford, S. Chekol, H.A. Young, A.B. Roberts, TGF- β and vitamin D3 Utilize Distinct pathways to suppress IL-12 production and modulate Rapid differentiation of human monocytes into CD83+ dendritic cells, *J. Immunol.* 174 (2005) 2061–2070, <https://doi.org/10.4049/jimmunol.174.4.2061>.
- [22] J.A. Hardin, Dendritic cells: potential triggers of autoimmunity and targets for therapy, *Ann. Rheum. Dis.* 64 (2005) iv86–iv90, <https://doi.org/10.1136/ard.2005.044560>.
- [23] C. Scanzzone, L. Agnello, G. Bivona, B. Lo Sasso, M. Ciaccio, Vitamin D and genetic susceptibility to multiple sclerosis, *Biochem. Genet.* 59 (2021), <https://doi.org/10.1007/s10528-020-10010-1>.
- [24] S. Gorman, L.A. Kuritzky, M.A. Judge, K.M. Dixon, J.P. McGlade, R.S. Mason, J.J. Finlay-Jones, P.H. Hart, Topically applied 1,25-dihydroxyvitamin D3 enhances the suppressive activity of CD4+CD25+ cells in the draining lymph nodes, *J. Immunol.* 179 (2007) 6273–6283, <https://doi.org/10.4049/jimmunol.179.9.6273>.
- [25] C. Daniel, N.A. Sartory, N. Zahn, H.H. Radeke, J.M. Stein, Immune modulatory treatment of trinitrobenzene sulfonic acid colitis with calcitriol is associated with a change of a T helper (Th) 1/Th17 to a Th2 and regulatory T cell profile, *J. Pharmacol. Exp. Ther.* 324 (2008) 23–33, <https://doi.org/10.1124/jpet.107.127209>.
- [26] S. Yu, M.T. Cantorna, The vitamin D receptor is required for iNKT cell development, *Proc. Natl. Acad. Sci. U. S. A.* 105 (2008) 5207–5212, <https://doi.org/10.1073/pnas.0711558105>.
- [27] C. Aranow, Vitamin D and the immune system, *J. Investig. Med. Off. Publ. Am. Fed. Clin. Res.* 59 (2011) 881–886, <https://doi.org/10.2310/JIM.0b013e31821b8755>.
- [28] C. Triantos, I. Aggeletopoulou, G.J. Mantzaris, A. Mouzaki, Molecular basis of vitamin D action in inflammatory bowel disease, *Autoimmun. Rev.* 21 (2022) 103136, <https://doi.org/10.1016/j.autrev.2022.103136>.
- [29] C.F. Pelajo, J.M. Lopez-Benitez, L.C. Miller, Vitamin D and autoimmune Rheumatologic disorders, *Autoimmun. Rev.* 9 (2010) 507–510, <https://doi.org/10.1016/j.autrev.2010.02.011>.
- [30] C.-Y. Yang, P.S.C. Leung, I.E. Adamopoulos, M.E. Gershwin, The implication of vitamin D and autoimmunity: a comprehensive review, *Clin. Rev. Allergy Immunol.* 45 (2013) 217–226, <https://doi.org/10.1007/s12016-013-8361-3>.
- [31] R. Saternus, S. Pilz, S. Gräber, M. Kleber, W. März, T. Vogt, J. Reichrath, A closer look at evolution: variants (SNPs) of genes involved in skin pigmentation, including exoc2, tyr, tyrp1, and dct, are associated with 25(OH)D serum concentration, *Endocrinology* 156 (2015) 39–47, <https://doi.org/10.1210/en.2014-1238>.
- [32] M.D. Kearns, J.A. Alvarez, N. Seidel, V. Tangpricha, V. Tangpricha, Impact of vitamin D on infectious disease, *Am. J. Med. Sci.* 349 (2015) 245–262, <https://doi.org/10.1097/MAJ.0000000000000360>.
- [33] A.G. Uitterlinden, Y. Fang, J.B.J. van Meurs, H.A.P. Pols, J.P.T.M. van Leeuwen, Genetics and biology of vitamin D receptor polymorphisms, *Gene* 338 (2004) 143–156, <https://doi.org/10.1016/j.gene.2004.05.014>.
- [34] M. Caliskan, C.D. Brown, J.C. Maranville, A catalog of GWAS fine-mapping efforts in autoimmune disease, *Am. J. Hum. Genet.* 108 (2021) 549–563, <https://doi.org/10.1016/j.ajhg.2021.03.009>.
- [35] M.J. Page, J.E. McKenzie, P.M. Bossuyt, I. Boutron, T.C. Hoffmann, C.D. Mulrow, L. Shamseer, J.M. Tetzlaff, E.A. Akl, S.E. Brennan, R. Chou, J. Glanville, J. M. Grimshaw, A. Hróbjartsson, M.M. Lalu, T. Li, E.W. Loder, E. Mayo-Wilson, S. McDonald, L.A. McGuinness, L.A. Stewart, J. Thomas, A.C. Tricco, V.A. Welch, P. Whiting, D. Moher, The PRISMA 2020 statement: an updated guideline for reporting systematic reviews, *BMJ* 372 (2021) n71, <https://doi.org/10.1136/bmj.n71>.
- [36] H. Yang, H. Lee, Research Trend Visualization by MeSH terms from PubMed, *Int. J. Environ. Res. Public Health* 15 (2018) 1113, <https://doi.org/10.3390/ijerph15061113>.
- [37] L. Najjar, J. Sutherland, A. Zhou, E. Hyppönen, Vitamin D and type 1 diabetes risk: a systematic review and meta-analysis of genetic evidence, *Nutrients* 13 (2021), <https://doi.org/10.3390/nu13124260>.
- [38] M. Karaky, A. Alcina, M. Fedetz, C. Barrionuevo, V. Potenciano, C. Delgado, G. Izquierdo, F. Matesanz, The multiple sclerosis-associated regulatory variant rs10877013 affects expression of CYP27B1 and VDR under inflammatory or Vitamin D stimuli, *Mult. Scler.* 22 (2016) 999–1006, <https://doi.org/10.1177/1352458515610208>.

- [39] M.B. Cox, M. Ban, N.A. Bowden, A. Baker, R.J. Scott, J. Lechner-Scott, Potential association of vitamin D receptor polymorphism Taq1 with multiple sclerosis, *Mult. Scler. J.* 18 (2012) 16–22, <https://doi.org/10.1177/1352458511415562>.
- [40] R. Lin, B. V Taylor, J. Charlesworth, I. van der Mei, L. Blizzard, N. Stewart, A.-L. Ponsonby, T. Dwyer, F. Pittas, S. Simpson, Modulating effects of WT1 on interferon- β -vitamin D association in MS, *Acta Neurol. Scand.* 131 (2015) 231–239, <https://doi.org/10.1111/ane.12315>.
- [41] R.A. Al-Temaimi, A. Al-Enezi, A. Al-Serri, R. Al-Roughani, F. Al-Mulla, The association of Vitamin D receptor polymorphisms with multiple sclerosis in a case-control study from Kuwait, *PLoS One* 10 (2015) 1–10, <https://doi.org/10.1371/journal.pone.0142265>.
- [42] D. Cierny, J. Michalik, M. Škeroňová, E. Kantorová, Š. Sivák, J. Javor, E. Kurča, D. Dobrota, J. Lehotský, ApaI, BsmI and TaqI VDR gene polymorphisms in association with multiple sclerosis in Slovaks, *Neurol. Res.* 38 (2016) 678–684, <https://doi.org/10.1080/01616412.2016.1200287>.
- [43] S.V. Ramagopalan, D.A. Dymant, M.Z. Cader, K.M. Morrison, G. Disanto, J.M. Morahan, A.J. Berlanga-Taylor, A. Handel, G.C. De Luca, A.D. Sadovnick, P. Lepage, A. Montpetit, G.C. Ebers, Rare variants in the CYP27B1 gene are associated with multiple sclerosis, *Ann. Neurol.* 70 (2011) 881–886, <https://doi.org/10.1002/ana.22678>.
- [44] L. Tajouri, M. Ovcarić, R. Curtain, M.P. Johnson, L.R. Griffiths, P. Csurhes, M.P. Pender, R.A. Lea, Variation in the vitamin D receptor gene is associated with multiple sclerosis in an Australian population, *J. Neurogenet.* 19 (2005) 25–38, <https://doi.org/10.1080/01677060590949692>.
- [45] P. Ostkamp, A. Salmen, B. Pignolet, D. Görlich, T.F.M. Andlauer, A. Schulte-Mecklenbeck, G. Gonzalez-Escamilla, F. Bucciarelli, I. Gennero, J. Breuer, G. Antony, T. Schneider-Hohendorf, N. Mykicky, A. Bayas, F. Then Bergh, S. Bittner, H.-P. Hartung, M.A. Friese, R.A. Linker, F. Luessi, K. Lehmann-Horn, M. Mühlau, F. Paul, M. Stangel, B. Tackenberg, H. Tuman, C. Warnke, F. Weber, B. Wildemann, U.K. Zettl, U. Ziemann, B. Müller-Myhok, T. Kimpfel, L. Klotz, S.G. Meuth, F. Zipp, B. Hemmer, R. Hohlfield, D. Brassat, R. Gold, C.C. Gross, C. Lukas, S. Groppa, K. Loser, H. Wiendl, N. Schwab, A. Bayas, S. Rothacher, S. Starke, F. Paul, J. Bellmann-Strobl, J. Behrens, J.-M. Dörr, R. Gieß, J. Kuchling, L. Rasche, R. Gold, A. Chan, G. Ellrichmann, A.L. Fisse, A. Gahlen, T. Grüter, A. Haghighi, R. Hoepner, Ü. Koc, C. Lukas, J. Motte, K. Pitarokoli, A. Salmen, R. Schneider, J. Schöllhammer, C. Schroeder, B. Ambrosius, S. Demir, C. Warnke, T. Dehmel, K. Ingenhoven, R. Linker, D.-H. Lee, A. Lämmer, E. Sauer, C. Heesen, J.-P. Stellmann, M. Stangel, L. Boenig, S. Ginge, M. Hümmert, P. Schwenkenbecher, T. Skripuletz, W. Suehs, B. Wildemann, M. Korporal-Kuhnke, H. Oßwald, A. Schwarz, A. Viehöver, V. Limmroth, K. Gerbershagen, F.T. Bergh, B. Ettrich, S. Gray, S. Haars, J. Orthgieß, N. Schwanitz, M. Stoppe, A. Unterlauff, S. Paryjas, S. Bittner, V. Fleischer, S. Groppa, F. Lüsi, J. Piepgras, T. Uphaus, B. Tackenberg, M. Pütz, C. Eienbröcker, M. Seipelt, R. Hohlfield, T. Kimpfel, J. Havla, I. Meinl, H. Pellkofer, E. Schuh, B. Hemmer, L. Aly, A. Berthele, V. Pongratz, K. Brinkhoff, D. Buck, C. Gasperi, M. Hermisson, M.-M. Hoshi, M. Kaminski, A. Klein, B. Knier, M. Kowarik, H. Kronsbein, K.L. Horn, M. Mitsdörffer, V. Pernpeintner, V. Rothhammer, A. Schweikert, R. Selzer, M. Mühlau, C. Zimmer, J. Kirschke, F. Weber, H. Staufner, M. Knop, S. Nischwitz, P. Sämann, H. Wiendl, S. Meuth, L. Klotz, G. Meyer zu Hörste, J. Krämer, L. Schünemann, C. Gross, S. Pfeuffer, T. Ruck, S. Belgriri, A. Buchheister, N. Büniger, K. Göbel, L. Kirstein, N. Melzer, O. Simon, A. Echterhoff, U. Zettl, A. Winkelmann, U. Ziemann, A. Abdelhak, M. Kowarik, M. Krumbholz, M. Paech, C. Ruschil, M.-I. Stefanou, J. Tünnerhoff, L. Zeltner, H. Sheikh, H. Tuman, T. Fangerau, F. Lauda, D. Rau, D. Taranu, A. Huss, D. Brassat, B. Pignolet, F. Bucciarelli, L. Scandella, C. Lebrun-Frenay, M. Deboverie, S. Pittion-Vouyovitch, B. Brochet, A. Ruet, G. Defer, N. Derache, J. de Sèze, D. Laplaud, S. Wiertlewski, O. Casez, P. Clavelou, P. Labauge, J. Pelletier, A. Rico, S. Vukusic, O. Outterryck, Jean-Claude, J.-C. Ouallet, P. Hauteceou, A. Tourbah, G. Castelno, E. Berger, H. Zéphir, P. Cabre, W. Camu, E. Thouvenot, T. Moreau, C. Papeix, C. Lubetzki, P. Vermersch, M. Cohen, L. Rumbach, Sunlight exposure exerts immunomodulatory effects to reduce multiple sclerosis severity, *Proc. Natl. Acad. Sci.* 118 (2021), <https://doi.org/10.1073/pnas.2018457118>.
- [46] A. Mostowska, M. Lianeri, M. Wudarski, M. Olesińska, P.P. Jagodziński, Vitamin D receptor gene BsmI, FokI, ApaI and TaqI polymorphisms and the risk of systemic lupus erythematosus, *Mol. Biol. Rep.* 40 (2013) 803–810, <https://doi.org/10.1007/s11033-012-2118-6>.
- [47] M.R. Meza-Meza, B. Vizmanos, M. Rivera-Escoto, A.I. Ruiz-Ballesteros, K. Pesqueda-Cendejas, I. Parra-Rojas, M. Montoya-Buelna, S. Luquín, B. Campos-López, P.E. Mora-García, S. Cerpa-Cruz, U. De la Cruz-Mosso, Vitamin D receptor (VDR) genetic variants: relationship of FokI genotypes with VDR expression and clinical disease activity in systemic lupus erythematosus patients, *Genes* 13 (2022) 2016, <https://doi.org/10.3390/genes13112016>.
- [48] H. Mahto, R. Tripathy, B.K. Das, A.K. Panda, Association between vitamin D receptor polymorphisms and systemic lupus erythematosus in an Indian cohort, *Int. J. Rheum. Dis.* 21 (2018) 468–476, <https://doi.org/10.1111/1756-185X.13245>.
- [49] O. Monticeli, J. Brenol, J. Chies, M. Longo, G. Rucatti, R. Scalco, R. Xavier, The role of Bsm I and Fok I vitamin D receptor gene polymorphisms and serum 25-hydroxyvitamin D in Brazilian patients with systemic lupus erythematosus, *Lupus* 21 (2012) 43–52, <https://doi.org/10.1177/0961203311421798>.
- [50] Y. Ozaki, S. Nomura, M. Nagahama, C. Yoshimura, H. Kagawa, S. Fukuhara, Vitamin-D receptor genotype and renal disorder in Japanese patients with systemic lupus erythematosus, *Nephron* 85 (2000) 86–91, <https://doi.org/10.1159/000045635>.
- [51] J. De Azevedo Silva, S.C. de Lima, T.S. Frago, C.A.J. Cavalcanti, A.D. Barbosa, M.E. de A. Borborema, T.M.C. de Lucena, A.L.B.P. Duarte, S. Crovella, P. Sandrin-Garcia, Differential distribution of vitamin D receptor (VDR) gene variants and its expression in systemic lupus erythematosus, *Int. J. Immunogenet.* 49 (2022) 181–192, <https://doi.org/10.1111/iji.12576>.
- [52] E. Ramos-Lopez, A. Kurylowicz, T. Bednarczyk, J. Paunkovic, C. Seidl, K. Badenhop, Vitamin D receptor polymorphisms are associated with Graves' disease in German and Polish but not in Serbian patients, *Thyroid* 15 (2005) 1125–1130, <https://doi.org/10.1089/thy.2005.15.1125>.
- [53] C. Panierakis, G. Goulielmos, D. Mamoulakis, E. Petraki, E. Papavasiliou, E. Galanakis, Vitamin D receptor gene polymorphisms and susceptibility to type 1 diabetes in Crete, Greece, *Clin. Immunol.* 133 (2009) 276–281, <https://doi.org/10.1016/j.clim.2009.08.004>.
- [54] M. Fichna, M. Zurawek, D. Januszkievicz-Lewandowska, P. Fichna, J. Nowak, PTPN22, PDCD1 and CYP27B1 polymorphisms and susceptibility to type 1 diabetes in Polish patients, *Int. J. Immunogenet.* 37 (2010) 367–372, <https://doi.org/10.1111/j.1744-313X.2010.00935.x>.
- [55] M.E. Miettinen, M.C. Smart, L. Kinnunen, C. Mathews, V. Harjutsalo, H.M. Surcel, C. Lamberger-Allardt, J. Tuomilehto, G.A. Hitman, Maternal VDR variants rather than 25-hydroxyvitamin D concentration during early pregnancy are associated with type 1 diabetes in the offspring, *Diabetologia* 58 (2015) 2278–2283, <https://doi.org/10.1007/s00125-015-3675-8>.
- [56] A.R. Van Der Slik, I. Van Den Eng, P. Eerligh, I.L.N. Doxiadis, B.P.C. Koeleman, B.O. Roep, M.J. Giphart, Sequence variation within the major histocompatibility complex subregion centromeric of HLA class II in type 1 diabetes, *Tissue Antigens* 69 (2007) 348–353, <https://doi.org/10.1111/j.1399-0039.2007.00820.x>.
- [57] R.S. Ferraz, C.S. Silva, G.C. Cavalcante, N.M. De Queiroz, K.M. Fel, S. Fel, A. Ribeiro-dos-santos, Variants in the VDR Gene May Influence 25 (OH) D Levels in Type 1 Diabetes Mellitus in a Brazilian Population, *vol. 25*, 2022.
- [58] S.U. Thorsen, H.B. Mortensen, B. Carstensen, M. Fenger, B.H. Thuesen, L. Husemoen, R. Bergholdt, C. Brorsson, F. Pociot, A. Linneberg, J. Svensson, No association between type 1 diabetes and genetic variation in vitamin D metabolism genes: a Danish study, *Pediatr. Diabetes* 15 (2014) 416–421, <https://doi.org/10.1111/pedi.12105>.
- [59] G. Tapia, K. Mårild, S.R. Dahl, N.A. Lund-Blix, M.K. Viken, B.A. Lie, P.R. Njølstad, G. Joner, T. Skriverhaug, A.S. Cohen, K. Størdal, L.C. Stene, Maternal and newborn Vitamin D-binding protein, Vitamin D levels, Vitamin D receptor genotype, and childhood type 1 diabetes, *Diabetes Care* 42 (2019) 553–559, <https://doi.org/10.2337/dc18-2176>.
- [60] M.A. Rasoul, M.Z. Haider, M. Al-Mahdi, H. Al-Kandari, G.S. Dhaunsi, Relationship of four vitamin D receptor gene polymorphisms with type 1 diabetes mellitus susceptibility in Kuwaiti children, *BMC Pediatr.* 19 (2019) 71, <https://doi.org/10.1186/s12887-019-1448-0>.
- [61] M. Vedralová, A. Kotrbová-Kozák, V. Železníková, H. Zoubková, I. Rychlík, M. Černá, Polymorphisms in the vitamin D receptor gene and Parathyroid hormone gene in the development and progression of diabetes mellitus and its chronic Complications, diabetic nephropathy and non-diabetic renal disease, *Kidney Blood Press. Res.* 36 (2012) 1–9, <https://doi.org/10.1159/000339021>.
- [62] M.J. Taverna, A. Sola, C. Guyot-Argenton, N. Pacher, F. Bruzzo, G. Slama, G. Reach, J.-L. Selam, Taq I polymorphism of the vitamin D receptor and risk of severe diabetic retinopathy, *Diabetologia* 45 (2002) 436–442, <https://doi.org/10.1007/s00125-001-0769-2>.
- [63] M. Pani, J. Seissler, K. Usadel, K. Badenhop, Vitamin D receptor genotype is associated with Addison's disease, *Eur. J. Endocrinol.* 147 (2002) 635–640, <https://doi.org/10.1530/eje.0.1470635>.
- [64] A. Latini, G. De Benedittis, C. Perricone, S. Colafrancesco, P. Conigliaro, F. Ceccarelli, M.S. Chimenti, L. Novelli, R. Priori, F. Conti, C. Ciccacci, P. Borgiani, VDR polymorphisms in autoimmune connective tissue diseases: Focus on Italian population, *J. Immunol. Res.* 2021 (2021) 1–6, <https://doi.org/10.1155/2021/5812136>.

- [65] B. Bugaj, J. Wielińska, J. Świerkot, K. Bogunia-Kubik, K. Górna, VDR polymorphic variants are related to Improvements in CRP and disease activity in patients with Axial Spondyloarthritis that Undergo Anti-TNF treatment, *Genes* 13 (2022) 1873, <https://doi.org/10.3390/genes13101873>.
- [66] K. Mårild, G. Tapia, M. Haugen, S.R. Dahl, A.S. Cohen, M. Lundqvist, B.A. Lie, L.C. Stene, K. Størdal, Maternal and neonatal vitamin D status, genotype and childhood celiac disease, *PLoS One* 12 (2017) e0179080, <https://doi.org/10.1371/journal.pone.0179080>.
- [67] J.L.S. Pedro, J.R. Bilbao, G. Perez de Nancrales, J.C. Vitoria, P. Martul, L. Castaño, Heterogeneity of vitamin D receptor gene association with celiac disease and type 1 diabetes mellitus, *Autoimmunity* 38 (2005) 439–444, <https://doi.org/10.1080/08916930500288455>.
- [68] M.A. Pani, A polymorphism within the vitamin D-binding protein gene is associated with Graves' disease but not with Hashimoto's thyroiditis, *J. Clin. Endocrinol. Metab.* 87 (2002) 2564–2567, <https://doi.org/10.1210/jc.87.6.2564>.
- [69] J. Djurovic, O. Stojkovic, O. Ozdemir, F. Silan, C. Akurut, J. Todorovic, K. Savic, G. Stamenkovic, Association between FokI, ApaI and TaqI RFLP polymorphisms in VDR gene and Hashimoto's thyroiditis: preliminary data from female patients in Serbia, *Int. J. Immunogenet.* 42 (2015) 190–194, <https://doi.org/10.1111/iji.12199>.
- [70] H.W.Z. Hanna, C. Rizzo, R.M. Abdel Halim, H.E. El Haddad, R. Salam, H. El-Sayed Abou-Youssef, Vitamin D status in Hashimoto's thyroiditis and its association with vitamin D receptor genetic variants, *J. Steroid Biochem. Mol. Biol.* 212 (2021) 105922, <https://doi.org/10.1016/j.jsbmb.2021.105922>.
- [71] S. Yesil, H.G. Tanyildiz, S.A. Tekgunduz, S. Toprak, A. Fettah, A.U. Dikmen, G. Sahin, Vitamin D receptor polymorphisms in immune thrombocytopenic purpura, *Pediatr. Int* 59 (2017) 682–685, <https://doi.org/10.1111/ped.13273>.
- [72] F. Marini, F. Falcini, S. Stagi, S. Fabbri, S. Ciuffi, D. Rigante, M.M. Cerinic, M.L. Brandi, Study of vitamin D status and vitamin D receptor polymorphisms in a cohort of Italian patients with juvenile idiopathic arthritis, *Sci. Rep.* 10 (2020) 17550, <https://doi.org/10.1038/s41598-020-74861-9>.
- [73] A. Maalej, E. Petit-Teixeira, L. Michou, A. Rebai, F. Cornelis, H. Ayadi, Association study of VDR gene with rheumatoid arthritis in the French population, *Genes Immun* 6 (2005) 707–711, <https://doi.org/10.1038/sj.gene.6364260>.
- [74] S. Yoshida, K. Ikari, T. Furuya, Y. Toyama, A. Taniguchi, H. Yamanaka, S. Momohara, A GC polymorphism associated with serum 25-hydroxyvitamin D level is a risk factor for hip fracture in Japanese patients with rheumatoid arthritis: 10-year follow-up of the Institute of Rheumatology, Rheumatoid Arthritis cohort study, *Arthritis Res. Ther.* 16 (2014) R75, <https://doi.org/10.1186/ar4516>.
- [75] M. Despotović, T. Jevtović Stojmenov, S. Stojanović, J. Bašić, J. Kundalić, B. Đorđević, M. Randelović, D. Pavlović, Association of vitamin D receptor genetic variants with bone mineral density and inflammatory markers in rheumatoid arthritis, *Clin. Biochem.* 87 (2021) 26–31, <https://doi.org/10.1016/j.clinbiochem.2020.10.006>.
- [76] M. Brink, L. Johansson, E. Nygren, L. Årlestig, J. Hultdin, S. Rantapää-Dahlqvist, Vitamin D in individuals before onset of rheumatoid arthritis - relation to vitamin D binding protein and its associated genetic variants, *BMC Rheumatol* 2 (2018) 26, <https://doi.org/10.1186/s41927-018-0033-8>.
- [77] Y.M. Hussien, A. Shehata, R.A. Karam, S.S. Alzahrani, H. Magdy, A.M. El-Shafey, Polymorphism in vitamin D receptor and osteoprotegerin genes in Egyptian rheumatoid arthritis patients with and without osteoporosis, *Mol. Biol. Rep.* 40 (2013) 3675–3680, <https://doi.org/10.1007/s11033-012-2443-9>.
- [78] S. Sobeih, H.M. Mashaly, H. Gawdat, K. Amr, M.F.A. Hamid, E. Shaalan, Evaluation of the correlation between serum levels of vitamin D and vitamin D receptor gene polymorphisms in an Egyptian population, *Int. J. Dermatol.* 55 (2016) 1329–1335, <https://doi.org/10.1111/ijd.13363>.
- [79] H. Irizar, M. Muñoz-Culla, O. Zuriarrain, E. Goyenechea, T. Castillo-Triviño, A. Prada, M. Saenz-Cuesta, D. De Juan, A. Lopez De Munain, J. Olasoaga, D. Otegui, HLA-DRB1*15:01 and multiple sclerosis: a female association? *Mult. Scler.* 18 (2012) 569–577, <https://doi.org/10.1177/1352458511426813>.
- [80] L. Agnello, C. Scizzzone, B. Lo Sasso, C. Bellia, G. Bivona, S. Realmuto, F. Frighina, R. Schillaci, G. Salemi, M. Ciacchio, VDBP, CYP27B1, and 25-hydroxyvitamin D gene polymorphism analyses in a group of Sicilian multiple sclerosis patients, *Biochem. Genet.* 55 (2017) 183–192, <https://doi.org/10.1007/s10528-016-9783-4>.
- [81] N. Barizzone, I. Pauwels, B. Luciano, D. Franckaert, F.R. Guerini, L. Cosmans, K. Hilven, A. Salvati, J. Dooley, D. Danso-Abeam, A. di Sapio, P. Cavalla, B. Decallonne, C. Mathieu, A. Liston, M. Leone, B. Dubois, S. D'Alfonso, A. Goris, No evidence for a role of rare CYP27B1 functional variations in multiple sclerosis, *Ann. Neurol.* 73 (2013) 433–437, <https://doi.org/10.1002/ana.23834>.
- [82] Ö. Ates, Analysis of vitamin D receptor (VDR) gene polymorphisms in Alopecia Areata, *J. Clin. Anal. Med.* 8 (2017) 151–154, <https://doi.org/10.4328/JCAM.4795>.
- [83] E. García-Martín, J.A.G. Agúndez, C. Martínez, J. Benito-León, J. Millán-Pascual, P. Calleja, M. Díaz-Sánchez, D. Pisa, L. Turpín-Fenoll, H. Alonso-Navarro, L. Ayuso-Peralta, D. Torrecillas, J.F. Plaza-Nieto, F.J. Jiménez-Jiménez, Vitamin D3 receptor (VDR) gene rs2228570 (FokI) and rs731236 (TaqI) variants are not associated with the risk for multiple sclerosis: results of a new study and a meta-analysis, *PLoS One* 8 (2013) e65487, <https://doi.org/10.1371/journal.pone.0065487>.
- [84] C. Scizzzone, L. Agnello, B. Lo Sasso, P. Ragonese, G. Bivona, S. Realmuto, G. Iacolino, C.M. Gambino, C. Bellia, G. Salemi, M. Ciacchio, Klotho and vitamin D in multiple sclerosis: an Italian study, *Arch. Med. Sci.* 16 (2020) 842–847, <https://doi.org/10.5114/aoms.2019.86969>.
- [85] C. Scizzzone, L. Agnello, B. Lo Sasso, G. Salemi, C.M. Gambino, P. Ragonese, G. Candore, A.M. Ciacchio, R.V. Giglio, G. Bivona, M. Vidali, M. Ciacchio, FOXP3 and GATA3 polymorphisms, vitamin D3 and multiple sclerosis, *Brain Sci.* 11 (2021) 415, <https://doi.org/10.3390/brainsci11040415>.
- [86] A. Hossein-nezhad, A. Spira, M.F. Holick, Influence of vitamin D status and vitamin D3 supplementation on genome wide expression of white blood cells: a randomized Double-Blind clinical trial, *PLoS One* 8 (2013) e58725, <https://doi.org/10.1371/journal.pone.0058725>.
- [87] G.K. Schwalfenberg, A review of the critical role of vitamin D in the functioning of the immune system and the clinical implications of vitamin D deficiency, *Mol. Nutr. Food Res.* 55 (2011) 96–108, <https://doi.org/10.1002/mnfr.201000174>.
- [88] H.F. DeLuca, Overview of general physiologic features and functions of vitamin D, *Am. J. Clin. Nutr.* 80 (2004) 1689S–1696S, <https://doi.org/10.1093/ajcn/80.6.1689S>.
- [89] A.I. Ruiz-Ballesteros, M.R. Meza-Meza, B. Vizmanos-Lamotte, I. Parra-Rojas, U. de la Cruz-Mosso, Association of vitamin D metabolism gene polymorphisms with autoimmunity: evidence in population genetic studies, *Int. J. Mol. Sci.* 21 (2020) 9626, <https://doi.org/10.3390/ijms21249626>.
- [90] M.M. Mendes, K.H. Hart, P.B. Botelho, S.A. Lanham-New, Vitamin D status in the tropics: is sunlight exposure the main determinant? *Nutr. Bull.* 43 (2018) 428–434, <https://doi.org/10.1111/nbu.12349>.
- [91] K.V. de S. de Santana, S.L. Oliver, M.M. Mendes, S. Lanham-New, K.E. Charlton, H. Ribeiro, Association between vitamin D status and lifestyle factors in Brazilian women: implications of sun exposure levels, Diet, and health, *EclinicalMedicine* 47 (2022) 101400, <https://doi.org/10.1016/j.eclim.2022.101400>.
- [92] R. Bouillon, Genetic and Racial differences in the vitamin D Endocrine system, *Endocrinol. Metab. Clin. North Am.* 46 (2017) 1119–1135, <https://doi.org/10.1016/j.ecl.2017.07.014>.
- [93] T.C. Chen, F. Chimeh, Z. Lu, J. Mathieu, K.S. Person, A. Zhang, N. Kohn, S. Martinello, R. Berkowitz, M.F. Holick, Factors that influence the cutaneous synthesis and dietary sources of vitamin D, *Arch. Biochem. Biophys.* 460 (2007) 213–217, <https://doi.org/10.1016/j.abb.2006.12.017>.
- [94] P. Jones, M. Lucock, G. Chaplin, N.G. Jablonski, M. Veysey, C. Scarlett, E. Beckett, Distribution of variants in multiple vitamin D-related loci (DHCR7/NADSYN1, GC, CYP2R1, CYP11A1, CYP24A1, VDR, RXRα and RXRγ) vary between European, East-Asian and Sub-Saharan African-ancestry populations, *Genes Nutr* 15 (2020) 5, <https://doi.org/10.1186/s12263-020-00663-3>.
- [95] X. Jiang, P.F. O'Reilly, H. Aschard, Y.H. Hsu, J.B. Richards, J. Dupuis, E. Ingelsson, D. Karasik, S. Pilz, Di Berry, B. Kestenbaum, J. Zheng, J. Luan, E. Sofianopoulou, E.A. Streeten, D. Albanes, P.L. Lutsey, L. Yao, W. Tang, M.J. Econs, H. Wallaschofski, H. Völzke, A. Zhou, C. Power, M.I. McCarthy, E. D. Michos, E. Boerwinkle, S.J. Weinstein, N.D. Freedman, W.Y. Huang, N.M. Van Schoor, N. Van Der Velde, L.C.P.G.M.D. Groot, A. Enneman, L.A. Cupples, S. L. Booth, R.S. Vasan, C.T. Liu, Y. Zhou, S. Ripatti, C. Ohlsson, L. Vandenput, M. Lorentzon, J.G. Eriksson, M.K. Shea, D.K. Houston, S.B. Kritchevsky, Y. Liu, K. K. Lohman, L. Ferrucci, M. Peacock, C. Gieger, M. Beekman, E. Slagboom, J. Deelen, Di Van Heemst, M.E. Kleber, W. März, I.H. De Boer, A.C. Wood, J.I. Rotter, S.S. Rich, C. Robinson-Cohen, M. Den Heijer, M.R. Jarvelin, A. Cavadinio, P.K. Joshi, J.F. Wilson, C. Hayward, L. Lind, K. Michaëlsson, S. Trompet, M. C. Zillikens, A.G. Uitterlinden, F. Rivadeneira, L. Broer, L. Zgaga, H. Campbell, E. Theodoratou, S.M. Farrington, M. Timofeeva, M.G. Dunlop, A.M. Valdes, E. Tikkani, T. Lehtimäki, L.P. Lytikäinen, M. Kähönen, O.T. Raitakari, V. Mikkilä, M.A. Ikram, N. Sattar, J.W. Jukema, N.J. Wareham, C. Langenberg, N. G. Forouhi, T.E. Gundersen, K.T. Khaw, A.S. Butterworth, J. Danesh, T. Spector, T.J. Wang, E. Hyppönen, P. Kraft, D.P. Kiel, Genome-wide association study in 79,366 European-ancestry individuals informs the genetic architecture of 25-hydroxyvitamin D levels, *Nat. Commun.* 9 (2018), <https://doi.org/10.1038/s41467-017-02662-2>.

- [96] T.J. Wang, F. Zhang, J.B. Richards, B. Kestenbaum, J.B. van Meurs, D. Berry, D.P. Kiel, E.A. Streeten, C. Ohlsson, D.L. Koller, L. Peltonen, J.D. Cooper, P. F. O'Reilly, D.K. Houston, N.L. Glazer, L. Vandenput, M. Peacock, J. Shi, F. Rivadeneira, M.I. McCarthy, P. Anneli, I.H. de Boer, M. Mangino, B. Kato, D. J. Smyth, S.L. Booth, P.F. Jacques, G.L. Burke, M. Goodarzi, C.-L. Cheung, M. Wolf, K. Rice, D. Goltzman, N. Hidiogrou, M. Ladouceur, N.J. Wareham, L. J. Hocking, D. Hart, N.K. Arden, C. Cooper, S. Malik, W.D. Fraser, A.-L. Hartikainen, G. Zhai, H.M. Macdonald, N.G. Forouhi, R.J. Loos, D.M. Reid, A. Hakim, E. Dennison, Y. Liu, C. Power, H.E. Stevens, L. Jaana, R.S. Vasan, N. Soranzo, J. Bojunga, B.M. Psaty, M. Lorentzon, T. Foroud, T.B. Harris, A. Hofman, J.-O. Jansson, J.A. Cauley, A.G. Uitterlinden, Q. Gibson, M.-R. Järvelin, D. Karasik, D.S. Siscovick, M.J. Econs, S.B. Kritchevsky, J.C. Florez, J.A. Todd, J. Dupuis, E. Hyppönen, T.D. Spector, Common genetic determinants of vitamin D insufficiency: a genome-wide association study, *Lancet* 376 (2010) 180–188, [https://doi.org/10.1016/S0140-6736\(10\)60588-0](https://doi.org/10.1016/S0140-6736(10)60588-0).
- [97] E. Puncėvičienė, J. Gaizevska, R. Sabaliauskaitė, L. Vencevičienė, A. Purienė, D. Vitkus, S. Jarmalaite, I. Butrimienė, Vitamin D and VDR gene polymorphisms' association with rheumatoid arthritis in Lithuanian population, *Medicina (B. Aires)* 57 (2021) 346, <https://doi.org/10.3390/medicina57040346>.
- [98] V. Boraska, V. Škrabić, E. Zeggini, C.J. Groves, M. Buljubašić, M. Peruzović, T. Zemunik, Family-based analysis of vitamin D receptor gene polymorphisms and type 1 diabetes in the population of South Croatia, *J. Hum. Genet.* 53 (2008) 210–214, <https://doi.org/10.1007/s10038-007-0234-2>.
- [99] M. Laplana, M. Sánchez-de-la-Torre, T. Puig, A. Caruz, J. Fibla, Vitamin-D pathway genes and HIV-1 disease progression in injection drug users, *Gene* 545 (2014) 163–169, <https://doi.org/10.1016/j.gene.2014.04.035>.
- [100] M.S. de la Torre, C. Torres, G. Nieto, S. Vergara, A.J. Carrero, J. Macías, J.A. Pineda, A. Caruz, J. Fibla, Vitamin D receptor gene haplotypes and susceptibility to HIV-1 infection in injection drug users, *J. Infect. Dis.* 197 (2008) 405–410, <https://doi.org/10.1086/525043>.
- [101] H. Arai, K.-I. Miyamoto, Y. Taketani, H. Yamamoto, Y. Iemori, K. Morita, T. Tonai, T. Nishisho, S. Mori, E. Takeda, A vitamin D receptor gene polymorphism in the translation initiation codon: effect on protein activity and relation to bone mineral density in Japanese women, *J. Bone Miner. Res.* 12 (1997) 915–921, <https://doi.org/10.1359/jbmr.1997.12.6.915>.
- [102] P.W. Jurutka, L.S. Remus, G.K. Whitfield, P.D. Thompson, J.-C. Hsieh, H. Zitzer, P. Tavakkoli, M.A. Galligan, H.T.L. Dang, C.A. Haussler, M.R. Haussler, The polymorphic N Terminus in human vitamin D receptor isoforms influences transcriptional activity by modulating interaction with transcription factor IIB, *Mol. Endocrinol.* 14 (2000) 401–420, <https://doi.org/10.1210/mend.14.3.0435>.
- [103] E. van Etten, L. Verlinden, A. Giulietti, E. Ramos-Lopez, D.D. Branisteau, G.B. Ferreira, L. Overbergh, A. Verstuyf, R. Bouillon, B.O. Roep, K. Badenhoop, C. Mathieu, The vitamin D receptor gene FokI polymorphism: functional impact on the immune system, *Eur. J. Immunol.* 37 (2007) 395–405, <https://doi.org/10.1002/eji.200636043>.
- [104] A. Shimada, Y. Kanazawa, Y. Motohashi, S. Yamada, T. Maruyama, H. Ikegami, T. Awata, E. Kawasaki, T. Kobayashi, K. Nakanishi, Y. Kawabata, S. Kurihara, M. Uga, S. Tanaka, Evidence for association between vitamin D receptor BsmI polymorphism and type 1 diabetes in Japanese, *J. Autoimmun.* 30 (2008) 207–211, <https://doi.org/10.1016/j.jaut.2007.09.002>.
- [105] S.F. Azab, Y.F. Ali, M.A.A. Farghaly, M.E. Hamed, M.A.N. Allah, A.A. Emam, N.I. Abdelsalam, M.I.A. Hashem, H.H. Gawish, R.M. Nabil, L.M. Kamel, D. S. Fahmy, S.F. Alsayed, N.M. Al Azizi, G.M. Al-Akad, M.A. Noah, H.M. Abdelrahman, A.R. Ahmed, E.A. Bendary, Vitamin D receptor gene BsmI polymorphisms in Egyptian children and adolescents with systemic lupus erythematosus, *Medicine (Baltimore)* 95 (2016) e5233, <https://doi.org/10.1097/MD.0000000000005233>.
- [106] C.-M. Huang, M.-C. Wu, J.-Y. Wu, F.-J. Tsai, Association of vitamin D receptor gene BsmI polymorphisms in Chinese patients with systemic lupus erythematosus, *Lupus* 11 (2002) 31–34, <https://doi.org/10.1191/0961203302lu1430a>.
- [107] X.-Y. Luo, M.-H. Yang, F.-X. Wu, L.-J. Wu, L. Chen, Z. Tang, N.-T. Liu, X.-F. Zeng, J.-L. Guan, G.-H. Yuan, Vitamin D receptor gene BsmI polymorphism B allele, but not BB genotype, is associated with systemic lupus erythematosus in a Han Chinese population, *Lupus* 21 (2012) 53–59, <https://doi.org/10.1177/0961203311422709>.
- [108] C. Carvalho, A. Marinho, B. Leal, A. Bettencourt, D. Boleixa, I. Almeida, F. Farinha, P.P. Costa, C. Vasconcelos, B.M. Silva, Association between vitamin D receptor (VDR) gene polymorphisms and systemic lupus erythematosus in Portuguese patients, *Lupus* 24 (2015) 846–853, <https://doi.org/10.1177/0961203314566636>.
- [109] M. Abbasi, Z. Rezaeizadzi, J.T. Afshari, M. Hatef, M. Sahebani, N. Saadati, Lack of association of vitamin D receptor gene BsmI polymorphisms in patients with systemic lupus erythematosus, *Rheumatol. Int.* 30 (2010) 1537–1539, <https://doi.org/10.1007/s00296-010-1504-4>.
- [110] O. Monticelo, J. Brenol, J. Chies, M. Longo, G. Rucatti, R. Scalco, S. Xavier, The role of Bsm I and Fok I vitamin D receptor gene polymorphisms and serum 25-hydroxyvitamin D in Brazilian patients with systemic lupus erythematosus, *Lupus* 21 (2012) 43–52, <https://doi.org/10.1177/0961203311421798>.
- [111] R.J.L. Martin, A.J. McKnight, C.C. Patterson, D.M. Sadlier, A.P. Maxwell, A rare haplotype of the vitamin D receptor gene is protective against diabetic nephropathy, *Nephrol. Dial. Transplant.* 25 (2010) 497–503, <https://doi.org/10.1093/ndt/gfp515>.
- [112] S. Nejentsev, J.D. Cooper, L. Godfrey, J.M.M. Howson, H. Rance, S. Nutland, N.M. Walker, C. Guja, C. Ionescu-Tirgoviste, D.A. Savage, D.E. Undlien, K. S. Rønningen, E. Tuomilehto-Wolf, J. Tuomilehto, K.M. Gillespie, S.M. Ring, D.P. Strachan, B. Widmer, D. Dunger, J.A. Todd, Analysis of the vitamin D receptor gene sequence variants in type 1 diabetes, *Diabetes* 53 (2004) 2709–2712, <https://doi.org/10.2337/diabetes.53.10.2709>.
- [113] C. Agliardi, F.R. Guerini, M. Saresella, D. Caputo, M.A. Leone, M. Zanzottera, E. Bolognesi, I. Marventano, N. Barizzone, M.E. Fasano, N. Al-Daghri, M. Clerici, Vitamin D receptor (VDR) gene SNPs influence VDR expression and modulate protection from multiple sclerosis in HLA-DRB1*15-positive individuals, *Brain Behav. Immun.* 25 (2011) 1460–1467, <https://doi.org/10.1016/j.bbi.2011.05.015>.
- [114] D.D. Bikle, Vitamin D metabolism, mechanism of action, and clinical applications, *Chem. Biol.* 21 (2014) 319–329, <https://doi.org/10.1016/j.chembiol.2013.12.016>.
- [115] C.E. Hayes, M.T. Cantorna, H.F. DeLuca, Vitamin D and multiple sclerosis, *Exp. Biol. Med.* 216 (1997) 21–27, <https://doi.org/10.3181/00379727-216-44153A>.
- [116] J.L. Dickinson, D.I. Perera, A.F. van der Mei, A.L. Ponsonby, A.M. Polanowski, R.J. Thomson, B.V. Taylor, J.D. McKay, J. Stankovich, T. Dwyer, Past environmental sun exposure and risk of multiple sclerosis: a role for the Cdx-2 Vitamin D receptor variant in this interaction, *Mult. Scler.* 15 (2009) 563–570, <https://doi.org/10.1177/1352458509102459>.
- [117] A. d'Alésio, M. Garabédian, J.P. Sabatier, G. Guaydier-Souquière, C. Marcelli, A. Lemaçon, O. Walrant-Debray, F. Jehan, Two single-nucleotide polymorphisms in the human vitamin D receptor promoter change protein–DNA complex formation and are associated with height and vitamin D status in adolescent girls, *Hum. Mol. Genet.* 14 (2005) 3539–3548, <https://doi.org/10.1093/hmg/ddi382>.
- [118] M. Kohlmeier, Kohlmeier M. NutriGenetics, Applying the Science of Personal Nutrition, Academic Press, San Diego, 2012, p. 386, 9-7801-2385-9-006, 2012, https://www.researchgate.net/publication/236687090_Kohlmeier_M_NutriGenetics_Applying_the_science_of_personal_nutrition_Academic_Press_San_Diego_2012_386_pp_ISBN_9-7801-2385-9-006.
- [119] C. Dessinioti, C. Antoniou, A. Katsambas, A.J. Stratigos, Melanocortin 1 receptor variants: functional role and pigmentary associations, *Photochem. Photobiol.* 87 (2011) 978–987, <https://doi.org/10.1111/j.1751-1097.2011.00970.x>.
- [120] J.M. Partridge, S.J.M. Weatherby, J.A. Woolmore, D.J. Highland, A.A. Fryer, C.L.A. Mann, M.D. Boggild, W.E.R. Ollier, R.C. Strange, C.P. Hawkins, Susceptibility and outcome in MS: associations with polymorphisms in pigmentation-related genes, *Neurology* 62 (2004) 2323–2325, <https://doi.org/10.1212/WNL.62.12.2323>.
- [121] T. Dwyer, I. Van Der Mei, A.L. Ponsonby, B.V. Taylor, J. Stankovich, J.D. McKay, R.J. Thomson, A.M. Polanowski, J.L. Dickinson, Melanocortin 1 receptor genotype, past environmental sun exposure, and risk of multiple sclerosis, *Neurology* 71 (2008) 583–589, <https://doi.org/10.1212/01.wnl.0000323928.57408.93>.
- [122] E. Healy, Functional variation of MC1R alleles from red-haired individuals, *Hum. Mol. Genet.* 10 (2001) 2397–2402, <https://doi.org/10.1093/hmg/10.21.2397>.
- [123] K.A. Beaumont, R.A. Newton, D.J. Smit, J.H. Leonard, J.L. Stow, R.A. Sturm, Altered cell surface expression of human MC1R variant receptor alleles associated with red hair and skin cancer risk, *Hum. Mol. Genet.* 14 (2005) 2145–2154, <https://doi.org/10.1093/hmg/ddi219>.
- [124] J.M. Gelfand, B.A.C. Cree, J. McElroy, J. Oksenberg, R. Green, E.M. Mowry, J.W. Miller, S.L. Hauser, A.J. Green, Vitamin D in African Americans with multiple sclerosis, *Neurology* 76 (2011) 1824–1830, <https://doi.org/10.1212/WNL.0b013e31821cccf5>.

- [125] T.A. Luger, T.E. Scholzen, T. Brzoska, M. Bohm, New insights into the functions of α -MSH and related peptides in the immune system, *Ann. N. Y. Acad. Sci.* 994 (2003) 133–140, <https://doi.org/10.1111/j.1749-6632.2003.tb03172.x>.
- [126] A.-L. Ponsonby, A. McMichael, I. van der Mei, Ultraviolet radiation and autoimmune disease: insights from epidemiological research, *Toxicology* 181–182 (2002) 71–78, [https://doi.org/10.1016/S0300-483X\(02\)00257-3](https://doi.org/10.1016/S0300-483X(02)00257-3).
- [127] J.A. Ellis, K.J. Scurrah, Y.R. Li, A.-L. Ponsonby, R.A. Chavez, A. Pezic, T. Dwyer, J.D. Akikusa, R.C. Allen, M.L. Becker, S.D. Thompson, B.A. Lie, B. Flatø, Ø. Førre, M. Punaro, C. Wise, T.H. Finkel, H. Hakonarson, J.E. Munro, Epistasis amongst PTPN2 and genes of the vitamin D pathway contributes to risk of juvenile idiopathic arthritis, *J. Steroid Biochem. Mol. Biol.* 145 (2015) 113–120, <https://doi.org/10.1016/j.jsbmb.2014.10.012>.
- [128] S. V. Ramagopalan, A. Heger, A.J. Berlanga, N.J. Maugeri, M.R. Lincoln, A. Burrell, L. Handunnetthi, A.E. Handel, G. Disanto, S.-M. Orton, C.T. Watson, J. M. Morahan, G. Giovannoni, C.P. Ponting, G.C. Ebers, J.C. Knight, A ChIP-seq defined genome-wide map of vitamin D receptor binding: associations with disease and evolution, *Genome Res.* 20 (2010) 1352–1360, <https://doi.org/10.1101/gr.107920.110>.
- [129] J. Ellis, K. Scurrah, R. Chavez, A. Ponsonby, A. Pezic, R. Allen, J. Akikusa, J. Munro, PReS-FINAL-2149: interaction of PTPN2 and vitamin D GC sequence variants and risk of juvenile idiopathic arthritis, *Pediatr. Rheumatol.* 11 (2013) P161, <https://doi.org/10.1186/1546-0096-11-S2-P161>.
- [130] B. Frederiksen, E. Liu, J. Romanos, A.K. Steck, X. Yin, M. Kroehl, T.E. Fingerlin, H. Erlich, G.S. Eisenbarth, M. Rewers, J.M. Norris, Investigation of the vitamin D receptor gene (VDR) and its interaction with protein tyrosine phosphatase, non-receptor type 2 gene (PTPN2) on risk of islet autoimmunity and type 1 diabetes: the Diabetes Autoimmunity Study in the Young (DAISY), *J. Steroid Biochem. Mol. Biol.* 133 (2013) 51–57, <https://doi.org/10.1016/j.jsbmb.2012.08.012>.
- [131] K.M. Doody, A. Bourdeau, M.L. Tremblay, T-cell protein tyrosine phosphatase is a key regulator in immune cell signaling: lessons from the knockout mouse model and implications in human disease, *Immunol. Rev.* 228 (2009) 325–341, <https://doi.org/10.1111/j.1600-065X.2008.00743.x>.
- [132] M. Scharl, P. Hruz, D.F. McCole, Protein Tyrosine Phosphatase non-Receptor Type 2 regulates IFN- γ -induced cytokine signaling in THP-1 monocytes, *Inflamm. Bowel Dis.* 16 (2010) 2055–2064, <https://doi.org/10.1002/ibd.21325>.
- [133] M.R. Spalinger, R. Manzini, L. Hering, J.B. Riggs, C. Gottier, S. Lang, K. Atrott, A. Fettelschoss, F. Olomski, T.M. Kündig, M. Fried, D.F. McCole, G. Rogler, M. Scharl, PTPN2 regulates inflammasome activation and controls onset of Intestinal inflammation and Colon cancer, *Cell Rep.* 22 (2018) 1835–1848, <https://doi.org/10.1016/j.celrep.2018.01.052>.
- [134] L. Hering, E. Katkeviciute, M. Schwarzfischer, P. Busenhardt, C. Gottier, D. Mrdjen, J. Komuczki, M. Wawrzyniak, S. Lang, K. Atrott, B. Becher, G. Rogler, M. Scharl, M.R. Spalinger, Protein tyrosine phosphatase non-receptor type 2 function in dendritic cells is crucial to Maintain tissue Tolerance, *Front. Immunol.* 11 (2020) 1–15, <https://doi.org/10.3389/fimmu.2020.01856>.
- [135] I. Santin, F. Moore, M.L. Colli, E.N. Gurzov, L. Marselli, P. Marchetti, D.L. Eizirik, PTPN2, a candidate gene for type 1 diabetes, Modulates Pancreatic β -cell Apoptosis via regulation of the BH3-only protein Bim, *Diabetes* 60 (2011) 3279–3288, <https://doi.org/10.2337/db11-0758>.
- [136] D.F. McCole, Regulation of epithelial barrier function by the inflammatory bowel disease candidate gene, PTPN2, *Ann. N. Y. Acad. Sci.* 1257 (2012) 108–114, <https://doi.org/10.1111/j.1749-6632.2012.06522.x>.
- [137] N. Bottini, E.J. Peterson, Tyrosine phosphatase PTPN22: Multifunctional regulator of immune signaling, development, and disease, *Annu. Rev. Immunol.* 32 (2014) 83–119, <https://doi.org/10.1146/annurev-immunol-032713-120249>.
- [138] R. Bouillon, F. Schuit, L. Antonio, F. Rastinejad, Vitamin D binding protein: a historic overview, *Front. Endocrinol.* 10 (2019) 910, <https://doi.org/10.3389/fendo.2019.00910>.
- [139] N. Yamamoto, V.R. Naraparaju, Role of vitamin D3-binding protein in activation of mouse macrophages, *J. Immunol.* 157 (1996) 1744–1749.
- [140] R. Bouillon, F.A. Van Assche, H. Van Baelen, W. Heyns, P. De Moor, Influence of the vitamin D-binding protein on the serum concentration of 1,25-dihydroxyvitamin D3, *J. Clin. Invest.* 67 (1981) 589–596, <https://doi.org/10.1172/JCI110072>.
- [141] A. Braun, R. Bichlmaier, B. Müller, H. Cleve, Molecular evaluation of an Alu repeat including a polymorphic variable poly(dA) (AluVpA) in the vitamin D binding protein (DBP) gene, *Hum. Genet.* 90 (1993) 526–532, <https://doi.org/10.1007/BF00217453>.
- [142] A. Braun, R. Bichlmaier, H. Cleve, Molecular analysis of the gene for the human vitamin-D-binding protein (group-specific component): allelic differences of the common genetic GC types, *Hum. Genet.* 89 (1992) 401–406, <https://doi.org/10.1007/BF00194311>.
- [143] J. Arnaud, J. Constans, Affinity differences for vitamin D metabolites associated with the genetic isoforms of the human serum carrier protein (DBP), *Hum. Genet.* 92 (1993) 183–188, <https://doi.org/10.1007/BF00219689>.
- [144] A. Sonnenberg, D.J. McCarty, S.J. Jacobsen, Geographic variation of inflammatory bowel disease within the United States, *Gastroenterology* 100 (1991) 143–149, [https://doi.org/10.1016/0016-5085\(91\)90594-B](https://doi.org/10.1016/0016-5085(91)90594-B).
- [145] H. Andraessen, J. Rungby, J.F. Dahlerup, L. Mosekilde, Inflammatory bowel disease and osteoporosis, *Scand. J. Gastroenterol.* 32 (1997) 1247–1255, <https://doi.org/10.3109/00365529709028155>.
- [146] J.J. Eloranta, C. Wenger, J. Mwyni, C. Hiller, C. Gubler, S.R. Vavricka, M. Fried, G.A. Kullak-Ublick, Association of a common vitamin D-binding protein polymorphism with inflammatory bowel disease, *Pharmacogenet. Genomics.* 21 (2011) 559–564, <https://doi.org/10.1097/FPC.0b013e328348f70c>.
- [147] A. Kurylowicz, E. Ramos-Lopez, T. Bednarczyk, K. Badenhop, Vitamin D-binding protein (DBP) gene polymorphism is associated with Graves' disease and the vitamin D status in a polish population study, *Exp. Clin. Endocrinol. Diabetes* 114 (2006) 329–335, <https://doi.org/10.1055/s-2006-924256>.
- [148] J.C. Ongagna, M. Pinget, A. Belcourt, Vitamin D-binding protein gene polymorphism association with IA-2 autoantibodies in type 1 diabetes, *Clin. Biochem.* 38 (2005) 415–419, <https://doi.org/10.1016/j.clinbiochem.2004.12.013>.
- [149] K. Batai, A.B. Murphy, E. Shah, M. Rude, J. Newsome, S. Agate, M.A. Dixon, H.Y. Chen, L.A. Deane, C.M.P. Hollowell, C. Ahaghotu, R.A. Kittles, Common vitamin D pathway gene variants reveal contrasting effects on serum vitamin D levels in African Americans and European Americans, *Hum. Genet.* 133 (2014) 1395–1405, <https://doi.org/10.1007/s00439-014-1472-y>.
- [150] G. Jones, D.E. Prosser, M. Kaufmann, Cytochrome P450-mediated metabolism of vitamin D, *J. Lipid Res.* 55 (2014) 13–31, <https://doi.org/10.1194/jlr.R031534>.
- [151] J.B. Cheng, M.A. Levine, N.H. Bell, D.J. Mangelsdorf, D.W. Russell, Genetic evidence that the human CYP2R1 enzyme is a key vitamin D 25-hydroxylase, *Proc. Natl. Acad. Sci.* 101 (2004) 7711–7715, <https://doi.org/10.1073/pnas.0402490101>.
- [152] A. Yarwood, P. Martin, J. Bowes, M. Lunt, J. Worthington, A. Barton, S. Eyre, Enrichment of vitamin D response elements in RA-associated loci supports a role for vitamin D in the pathogenesis of RA, *Genes Immun* 14 (2013) 325–329, <https://doi.org/10.1038/gene.2013.23>.
- [153] C. Scanzzone, L. Agnello, P. Ragonese, B. Lo Sasso, C. Bellia, G. Bivona, R. Schillaci, G. Salemi, M. Ciccio, Association of CYP2R1 rs10766197 with MS risk and disease progression, *J. Neurosci. Res.* 96 (2018) 297–304, <https://doi.org/10.1002/jnr.24133>.
- [154] E. Ramos-Lopez, P. Brück, T. Jansen, J. Herwig, K. Badenhop, CYP2R1 (vitamin D 25-hydroxylase) gene is associated with susceptibility to type 1 diabetes and vitamin D levels in Germans, *Diabetes, Metab. Res. Rev.* 23 (2007) 631–636, <https://doi.org/10.1002/dmrr.719>.
- [155] J.T. Almeida, D. Rodrigues, J. Guimarães, M.C. Lemos, Vitamin d pathway genetic variation and type 1 diabetes: a case-control association study, *Genes* 11 (2020) 1–7, <https://doi.org/10.3390/genes11080897>.
- [156] M.A. Al-Barry, A.M. Albalawi, M.A. Sayf, A. Badawi, S. Afzal, M. Latif, M.I. Samman, S. Basit, Sequence analysis of four vitamin D family genes (VDR, CYP24A1, CYP27B1 and CYP2R1) in Vogt-Koyanagi-Harada (VKH) patients: identification of a potentially pathogenic variant in CYP2R1, *BMC Ophthalmol.* 16 (2016) 172, <https://doi.org/10.1186/s12886-016-0354-6>.
- [157] M. Wjst, J. Altmüller, T. Faus-Kessler, C. Braig, M. Bahnweg, E. André, Asthma families show transmission disequilibrium of gene variants in the vitamin D metabolism and signalling pathway, *Respir. Res.* 7 (2006) 60, <https://doi.org/10.1186/1465-9921-7-60>.
- [158] A. Arabi, N. Khoueiry-Zgheib, Z. Awada, R. Mahfouz, L. Al-Shaar, M. Hoteit, M. Rahme, R. Baddoura, G. Halabi, R. Singh, G. El Hajj Fuleihan, CYP2R1 polymorphisms are important modulators of circulating 25-hydroxyvitamin D levels in elderly females with vitamin insufficiency, but not of the response to vitamin D supplementation, *Osteoporos. Int.* 28 (2017) 279–290, <https://doi.org/10.1007/s00198-016-3713-5>.
- [159] D. Manousaki, A. Harrou, R.E. Mitchell, S. Ross, V. Forgetta, N.J. Timpson, G.D. Smith, C. Polychronakos, J.B. Richards, Vitamin D levels and risk of type 1 diabetes: a Mendelian randomization study, *PLoS Med.* 18 (2021) e1003536, <https://doi.org/10.1371/journal.pmed.1003536>.

- [160] M. Fichna, M. Żurawek, D. Januszkiewicz-Lewandowska, M. Gryczyńska, P. Fichna, J. Sowiński, J. Nowak, Association of the CYP27B1 C(−1260)A polymorphism with autoimmune Addison's disease, *Exp. Clin. Endocrinol. Diabetes* 118 (2009) 544–549, <https://doi.org/10.1055/s-00029-1241206>.
- [161] E.R. Lopez, K. Regulla, M.A. Pani, M. Krause, K.-H. Usadel, K. Badenhoop, CYP27B1 polymorphisms variants are associated with type 1 diabetes mellitus in Germans, *J. Steroid Biochem. Mol. Biol.* 89–90 (2004) 155–157, <https://doi.org/10.1016/j.jsbmb.2004.03.095>.
- [162] J.C. Zhuang, Z.Y. Huang, G.X. Zhao, H. Yu, Z.X. Li, Z.Y. Wu, Variants of CYP27B1 are associated with both multiple sclerosis and neuromyelitis optica patients in Han Chinese population, *Gene* 557 (2015) 236–239, <https://doi.org/10.1016/j.gene.2014.12.045>.
- [163] E. Lopez, O. Zwermann, M. Segni, G. Meyer, M. Reincke, J. Seissler, J. Herwig, K. Usadel, K. Badenhoop, A promoter polymorphism of the CYP27B1 gene is associated with Addison's disease, Hashimoto's thyroiditis, Graves' disease and type 1 diabetes mellitus in Germans, *Eur. J. Endocrinol.* 151 (2004) 193–197, <https://doi.org/10.1530/eje.0.1510193>.
- [164] A. Kurylowicz, K. Badenhoop, CYP27B1 gene polymorphism is associated with Graves' disease in a polish population study, *Thyroid* 15 (2005) 1107–1108, <https://doi.org/10.1089/thy.2005.15.1107>.
- [165] D.K. Panda, D. Miao, M.L. Tremblay, J. Sirois, R. Farookhi, G.N. Hendy, D. Goltzman, Targeted ablation of the 25-hydroxyvitamin D 1 α -hydroxylase enzyme: evidence for skeletal, reproductive, and immune dysfunction, *Proc. Natl. Acad. Sci.* 98 (2001) 7498–7503, <https://doi.org/10.1073/pnas.131029498>.
- [166] C.J. Kim, L.E. Kaplan, F. Perwad, N. Huang, A. Sharma, Y. Choi, W.L. Miller, A.A. Portale, Vitamin D 1 α -hydroxylase gene Mutations in patients with 1 α -hydroxylase deficiency, *J. Clin. Endocrinol. Metab.* 92 (2007) 3177–3182, <https://doi.org/10.1210/jc.2006-2664>.
- [167] J.T. Wang, C.-J. Lin, S.M. Burridge, G.K. Fu, M. Labuda, A.A. Portale, W.L. Miller, Genetics of vitamin D 1 α -hydroxylase deficiency in 17 families, *Am. J. Hum. Genet.* 63 (1998) 1694–1702, <https://doi.org/10.1086/302156>.
- [168] R. Bailey, J.D. Cooper, D.J. Smyth, J.H.M. Yang, N.M. Walker, E. Hyppönen, D.B. Dunger, E. Ramos-Lopez, K. Badenhoop, S. Nejentsev, J.A. Todd, Association of the vitamin D metabolism gene CYP27B1 with type 1 diabetes, *Diabetes* 56 (2007) 2616–2621, <https://doi.org/10.2337/db07-0652>.
- [169] H. Arai, K.I. Miyamoto, M. Yoshida, H. Yamamoto, Y. Taketani, K. Morita, M. Kubota, S. Yoshida, M. Ikeda, F. Watabe, Y. Kanemasa, E. Takeda, The polymorphism in the caudal-related homeodomain protein Cdx-2 binding element in the human vitamin D receptor gene, *J. Bone Miner. Res.* 16 (2001) 1256–1264, <https://doi.org/10.1359/jbmr.2001.16.7.1256>.
- [170] D.P. Hayes, Vitamin D and ageing, *Biogerontology* 11 (2010) 1–16, <https://doi.org/10.1007/s10522-009-9252-0>.
- [171] M. Laplana, M. Sánchez-de-la-Torre, A. Aguiló, I. Casado, M. Flores, R. Sánchez-Pellicer, J. Fibla, Tagging long-lived individuals through vitamin-D receptor (VDR) haplotypes, *Biogerontology* 11 (2010) 437–446, <https://doi.org/10.1007/s10522-010-9273-8>.
- [172] S.S. Khayyatzaheh, M. Mehrmiz, H. Esmaily, S.J. Mirmousavi, L. Khajavi, F.N. Salehkhani, P. Hanachi, H. Bahrami-Taghanaki, S. Eslami, H. Vatanparast, G. A. Ferns, A. Avan, M. Ghayour-Mobarhan, A variant in CYP27B1 predicts circulating vitamin D levels after supplementation with high-dose of vitamin D in healthy adolescent girls, *J. Cell. Physiol.* 234 (2019) 13977–13983, <https://doi.org/10.1002/jcp.28083>.
- [173] A. Bahrami, M. Mehrmiz, M. Ghayour-Mobarhan, H. Bahrami-Taghanaki, K. Sadeghi Ardekani, M. Tayefi, M. Sadeghzade, M. Rashidmayvan, M. Safari Ghalezou, G.A. Ferns, A. Avan, H.R. Sadeghnia, A genetic variant in the cytochrome P450 family 2 subfamily R member 1 determines response to vitamin D supplementation, *Clin. Nutr.* 38 (2019) 676–681, <https://doi.org/10.1016/j.clnu.2018.03.018>.
- [174] M. Ammar, S. Heni, M.S. Tira, Y. Khalij, H. Hamdouni, D. Amor, S. Ksibi, A. Omezzine, A. Bouslama, Variability in response to vitamin D supplementation according to vitamin D metabolism related gene polymorphisms in healthy adults, *Eur. J. Clin. Nutr.* 77 (2023) 189–194, <https://doi.org/10.1038/s41430-022-01218-y>.
- [175] A. Harroud, D.A. Hafler, Common genetic factors among autoimmune diseases, *Science* 380 (2023) 485–490, <https://doi.org/10.1126/science.adg2992>, 80.
- [176] A. Gusev, S.H. Lee, G. Trynka, B.J. Vilhjálmsson, H. Xu, C. Zang, S. Ripke, B. Bulik-Sullivan, E. Stahl, A.K. Kähler, C.M. Hultman, S.M. Purcell, S. A. McCarroll, M. Daly, B. Pasaniuc, P.F. Sullivan, B.M. Neale, N.R. Wray, S. Raychaudhuri, A.L. Price, S. Ripke, B.M. Neale, A. Corvin, J.T.R. Walters, K.-H. Farh, P.A. Holmans, P. Lee, B. Bulik-Sullivan, D.A. Collier, H. Huang, T.H. Pers, I. Agartz, E. Agerbo, M. Albus, M. Alexander, F. Amin, S.A. Bacanu, M. Begemann, R.A. Belliveau, J. Bene, S.E. Bergen, E. Bevilacqua, T.B. Bigdeli, D.W. Black, A.D. Börglum, R. Bruggeman, N.G. Buccola, R.L. Buckner, W. Byerley, W. Cahn, G. Cai, D. Campion, R.M. Cantor, V.J. Carr, N. Carrera, S.V. Catts, K.D. Chambert, R.C.K. Chan, R.Y.L. Chen, E.Y.H. Chen, W. Cheng, E.F. C. Cheung, S.A. Chong, C.R. Cloninger, D. Cohen, N. Cohen, P. Cormican, N. Craddock, J.J. Crowley, D. Curtis, M. Davidsson, K.L. Davis, F. Degenhardt, J. Del Favero, L.E. DeLisi, D. Demontis, D. Dikeos, T. Dinan, S. Djurovic, G. Donohoe, E. Drapeau, J. Duan, F. Dudbridge, N. Durmishi, P. Eichhammer, J. Eriksson, V. Escott-Price, L. Essioux, A.H. Fanous, M.S. Farrell, J. Frank, L. Franke, R. Freedman, N.B. Freimer, M. Friedl, J.I. Friedman, M. Fromer, G. Genovese, L. Georgieva, E.S. Gershon, I. Giegling, P. Giusti-Rodriguez, S. Godard, J.I. Goldstein, V. Golimbet, S. Gopal, J. Gratten, J. Grove, L. de Haan, C. Hammer, M. L. Hamshere, M. Hansen, T. Hansen, V. Haroutunian, A.M. Hartmann, F.A. Henskens, S. Herms, J.N. Hirschhorn, P. Hoffmann, A. Hofman, M.V. Hollegaard, D. M. Hougaard, M. Ikeda, I. Joa, A. Julià, R.S. Kahn, L. Kalaydjieva, S. Karachanov-Yankova, J. Karjalainen, D. Kavanagh, M.C. Keller, B.J. Kelly, J.L. Kennedy, A. Khrunin, Y. Kim, J. Klavins, J.A. Knowles, B. Konte, V. Kucinskias, Z.A. Kucinskienė, H. Kuzelova-Ptackova, A.K. Kähler, C. Laurent, J.L.C. Keong, S.H. Lee, S. E. Legge, B. Lerer, M. Li, T. Li, K.-Y. Liang, J. Lieberman, S. Limborska, C.M. Loughland, J. Lubinski, J. Linnqvist, M. Macek, P.K.E. Magnusson, B.S. Maher, W. Maier, J. Mallet, S. Marsal, M. Mattheisen, M. Mattingdal, R.W. McCarley, C. McDonald, A.M. McIntosh, S. Meier, C.J. Meijer, B. Melegh, I. Melle, R. I. Mesulam-Gately, A. Metspalu, P.T. Michie, L. Milani, V. Milanova, Y. Mokrab, D.W. Morris, O. Mors, P.B. Mortensen, K.C. Murphy, R.M. Murray, I. Myin-Germeyns, B. Miller-Myhosh, M. Nelis, I. Nenadic, D.A. Nertney, G. Nestadt, K.K. Nicodemus, L. Nikitina-Zake, L. Nisenbaum, A. Nordin, E. O'Callaghan, C. O'Dushlaine, F.A. O'Neill, S.-Y. Oh, A. Olincy, L. Olsen, J. Van Os, C. Pantelis, G.N. Papadimitriou, S. Papiol, E. Parkhomenko, M.T. Pato, T. Paunio, M. Pejovic-Milovancevic, D.O. Perkins, O. Pietilinen, J. Pimm, A.J. Pocklington, J. Powell, A. Price, A.E. Pulver, S.M. Purcell, D. Quesed, H.B. Rasmussen, A. Reichenberg, M.A. Reimers, A.L. Richards, J.L. Roffman, P. Roussos, D.M. Ruderfer, V. Salomaa, A.R. Sanders, U. Schall, C.R. Schubert, T.G. Schulze, S. G. Schwab, E.M. Scolnick, R.J. Scott, L.J. Seidman, J. Shi, E. Sigurdsson, T. Silagadze, J.M. Silverman, K. Sim, P. Slominsky, J.W. Smoller, H.-C. So, C.C. A. Spencer, E.A. Stahl, H. Stefansson, S. Steinberg, E. Stogmann, R.E. Straub, E. Strengman, J. Strohmaier, T.S. Stroup, M. Subramaniam, J. Suvisaari, D. M. Svrakic, J.P. Szatkiewicz, E. Sderman, S. Thirumalai, D. Toncheva, P.A. Tooney, S. Tosato, J. Veijola, J. Waddington, D. Walsh, D. Wang, Q. Wang, B. T. Webb, M. Weiser, D.B. Wildenauer, N.M. Williams, S. Witt, A.R. Wolen, E.H.M. Wong, B.K. Wormley, J.Q. Wu, H.S. Xi, C.C. Zai, X. Zheng, F. Zimprich, N.R. Wray, K. Stefansson, P.M. Visscher, R. Adolfsson, O.A. Andreassen, D.H.R. Blackwood, E. Bramer, J.D. Buxbaum, A.D. Brglum, S. Cichon, A. Darvasi, E. Domenici, H. Ehrenreich, T. Esko, P.V. Gejman, M. Gill, H. Gurling, C.M. Hultman, N. Iwata, A.V. Jablensky, E.G. Jönsson, K.S. Kendler, G. Kirov, J. Knight, T. Lencz, D.F. Levinson, Q.S. Li, J. Liu, A.K. Malhotra, S.A. McCarroll, A. McQuillin, J.L. Moran, P.B. Mortensen, B.J. Mowry, M.M. Nthen, R. A. Ophoff, M.J. Owen, A. Palotie, C.N. Pato, T.L. Petryshen, D. Posthuma, M. Rietschel, B.P. Riley, D. Rujescu, P.C. Sham, P. Sklar, D. St Clair, D.R. Weinberger, J.R. Wendland, T. Werge, M.J. Daly, P.F. Sullivan, M.C. O'Donovan, S. Ripke, C. O'Dushlaine, K. Chambert, J.L. Moran, A.K. Kähler, S. Akterin, S. Bergen, P.K. E. Magnusson, B.M. Neale, D. Ruderfer, E. Scolnick, S. McCarroll, P. Sklar, C.M. Hultman, P.F. Sullivan, Partitioning heritability of regulatory and cell-type-specific variants across 11 common diseases, *Am. J. Hum. Genet.* 95 (2014) 535–552, <https://doi.org/10.1016/j.ajhg.2014.10.004>.

REFERENCES

- [177] H. Irizar, et al., HLA-DRB1*15:01 and multiple sclerosis: a female association? *Mult. Scler. J.* 18 (2012) 569–577.
- [178] L. Agnello, et al., VDBP, CYP27B1, and 25-hydroxyvitamin D gene polymorphism analyses in a group of Sicilian multiple sclerosis patients, *Biochem. Genet.* 55 (2017) 183–192.
- [179] M. Karaky, et al., The multiple sclerosis-associated regulatory variant rs10877013 affects expression of CYP27B1 and VDR under inflammatory or Vitamin D stimuli, *Mult. Scler.* 22 (2016) 999–1006.
- [180] M.B. Cox, et al., Potential association of vitamin D receptor polymorphism Taq1 with multiple sclerosis, *Mult. Scler. J.* 18 (2012) 16–22.
- [181] C. Scanzone, et al., Association of CYP2R1 rs10766197 with MS risk and disease progression, *J. Neurosci. Res.* 96 (2018) 297–304.
- [182] R. Lin, et al., Modulating effects of WT1 on interferon- β -vitamin D association in MS, *Acta Neurol. Scand.* 131 (2015) 231–239.
- [183] R.A. Al-Temaimi, A. Al-Enezi, A. Al-Serri, R. Al-Roughani, F. Al-Mulla, The association of Vitamin D receptor polymorphisms with multiple sclerosis in a case-control study from Kuwait, *PLoS One* 10 (2015) 1–10.

- [184] E. García-Martín, et al., Vitamin D3 receptor (VDR) gene rs2228570 (FokI) and rs731236 (TaqI) variants are not associated with the risk for multiple sclerosis: results of a new study and a meta-analysis, *PLoS One* 8 (2013).
- [185] D. Čierny, et al., ApaI, BsmI and TaqI VDR gene polymorphisms in association with multiple sclerosis in Slovaks, *Neurol. Res.* 38 (2016) 678–684.
- [186] S.V. Ramagopalan, et al., Rare variants in the CYP27B1 gene are associated with multiple sclerosis, *Ann. Neurol.* 70 (2011) 881–886.
- [187] J.L. Dickinson, et al., Past environmental sun exposure and risk of multiple sclerosis: a role for the Cdx-2 Vitamin D receptor variant in this interaction, *Mult. Scler.* 15 (2009) 563–570.
- [188] N. Barizzzone, et al., No evidence for a role of rare CYP27B1 functional variations in multiple sclerosis, *Ann. Neurol.* 73 (2013) 433–437.
- [189] T. Dwyer, et al., Melanocortin 1 receptor genotype, past environmental sun exposure, and risk of multiple sclerosis, *Neurology* 71 (2008) 583–589.
- [190] L. Tajouri, et al., Variation in the vitamin D receptor gene is associated with multiple sclerosis in an Australian population, *J. Neurogenet.* 19 (2005) 25–38.
- [191] J.C. Zhuang, et al., Variants of CYP27B1 are associated with both multiple sclerosis and neuromyelitis optica patients in Han Chinese population, *Gene* 557 (2015) 236–239.
- [192] P. Ostkamp, et al., Sunlight exposure exerts immunomodulatory effects to reduce multiple sclerosis severity, *Proc. Natl. Acad. Sci.* 118 (2021).
- [193] C. Scazzone, et al., Klotho and vitamin D in multiple sclerosis: an Italian study, *Arch. Med. Sci.* 16 (2020) 842–847.
- [194] C. Scazzone, et al., FOXP3 and GATA3 polymorphisms, vitamin D3 and multiple sclerosis, *Brain Sci.* 11 (2021) 415.
- [195] A. Mostowska, M. Lianeri, M. Wudarski, M. Olesińska, P.P. Jagodziński, Vitamin D receptor gene BsmI, FokI, ApaI and TaqI polymorphisms and the risk of systemic lupus erythematosus, *Mol. Biol. Rep.* 40 (2013) 803–810.
- [196] M.R. Meza-Meza, et al., Vitamin D receptor (VDR) genetic variants: relationship of FokI genotypes with VDR expression and clinical disease activity in systemic lupus erythematosus patients, *Genes* 13 (2022) 2016.
- [197] S.F. Azab, et al., Vitamin D receptor gene BsmI polymorphisms in Egyptian children and adolescents with systemic lupus erythematosus: a case-control study, *Med. (United States)* 95 (2016).
- [198] H. Mahto, R. Tripathy, B.K. Das, A.K. Panda, Association between vitamin D receptor polymorphisms and systemic lupus erythematosus in an Indian cohort, *Int. J. Rheum. Dis.* 21 (2018) 468–476.
- [199] O.A. Monticelo, et al., The role of BsmI and FokI vitamin D receptor gene polymorphisms and serum 25-hydroxyvitamin D in Brazilian patients with systemic lupus erythematosus, *Lupus* 21 (2012) 43–52.
- [200] Y. Ozaki, et al., Vitamin-D receptor genotype and renal disorder in Japanese patients with systemic lupus erythematosus, *Nephron* 85 (2000) 86–91.
- [201] J. De Azevedo Silva, et al., Differential distribution of vitamin D receptor (VDR) gene variants and its expression in systemic lupus erythematosus, *Int. J. Immunogenet.* 49 (2022) 181–192.
- [202] E. Ramos-Lopez, P. Brück, T. Jansen, J. Herwig, K. Badenhop, CYP2R1 (vitamin D 25-hydroxylase) gene is associated with susceptibility to type 1 diabetes and vitamin D levels in Germans, *Diabetes. Metab. Res. Rev.* 23 (2007) 631–636.
- [203] C. Panierakis, et al., Vitamin D receptor gene polymorphisms and susceptibility to type 1 diabetes in Crete, Greece, *Clin. Immunol.* 133 (2009) 276–281.
- [204] M. Fichna, M. Zurawek, D. Januszkiewicz-Lewandowska, P. Fichna, J.P.T.N.22 Nowak, PDCD1 and CYP27B1 polymorphisms and susceptibility to type 1 diabetes in Polish patients, *Int. J. Immunogenet.* 37 (2010) 367–372.
- [205] S. Nejentsev, et al., Analysis of the vitamin D receptor gene sequence variants in type 1 diabetes, *Diabetes* 53 (2004) 2709–2712.
- [206] R. Bailey, et al., Association of the vitamin D metabolism gene CYP27B1 with type 1 diabetes, *Diabetes* 56 (2007) 2616–2621.
- [207] M.E. Miettinen, et al., Maternal VDR variants rather than 25-hydroxyvitamin D concentration during early pregnancy are associated with type 1 diabetes in the offspring, *Diabetologia* 58 (2015) 2278–2283.
- [208] V. Boraska, et al., Family-based analysis of vitamin D receptor gene polymorphisms and type 1 diabetes in the population of South Croatia, *J. Hum. Genet.* 53 (2008) 210–214.
- [209] J.C. Ongagna, M. Pinget, A. Belcourt, Vitamin D-binding protein gene polymorphism association with IA-2 autoantibodies in type 1 diabetes, *Clin. Biochem.* 38 (2005) 415–419.
- [210] E.R. Lopez, et al., CYP27B1 polymorphisms variants are associated with type 1 diabetes mellitus in Germans, *J. Steroid Biochem. Mol. Biol.* 89–90 (2004) 155–157.
- [211] A.R. Van Der Slik, et al., Sequence variation within the major histocompatibility complex subregion centromeric of HLA class II in type 1 diabetes, *Tissue Antigens* 69 (2007) 348–353.
- [212] R.S. Ferraz, et al., Variants in the VDR gene may influence 25 (OH) D levels in type 1 diabetes mellitus in a Brazilian population 25 (2022).
- [213] J.T. Almeida, D. Rodrigues, J. Guimarães, M.C. Lemos, Vitamin d pathway genetic variation and type 1 diabetes: a case-control association study, *Genes* 11 (2020) 1–7.
- [214] S.U. Thorsen, et al., No association between type 1 diabetes and genetic variation in vitamin D metabolism genes: a Danish study, *Pediatr. Diabetes* 15 (2014) 416–421.
- [215] G. Tapia, et al., Maternal and newborn Vitamin D-binding protein, Vitamin D levels, Vitamin D receptor genotype, and childhood type 1 diabetes, *Diabetes Care* 42 (2019) 553–559.
- [216] M.A. Rasoul, M.Z. Haider, M. Al-Mahdi, H. Al-Kandari, G.S. Dhaunsi, Relationship of four vitamin D receptor gene polymorphisms with type 1 diabetes mellitus susceptibility in Kuwaiti children, *BMC Pediatr.* 19 (2019) 71.
- [217] M. Vedralová, et al., Polymorphisms in the vitamin D receptor gene and Parathyroid hormone gene in the development and progression of diabetes mellitus and its chronic Complications, diabetic nephropathy and non-diabetic renal disease, *Kidney Blood Press. Res.* 36 (2012) 1–9.
- [218] B. Frederiksen, et al., Investigation of the vitamin D receptor gene (VDR) and its interaction with protein tyrosine phosphatase, non-receptor type 2 gene (PTPN2) on risk of islet autoimmunity and type 1 diabetes: the Diabetes Autoimmunity Study in the Young (DAISY), *J. Steroid Biochem. Mol. Biol.* 133 (2013) 51–57.
- [219] R.J.L. Martin, A.J. McKnight, C.C. Patterson, D.M. Sadlier, A.P. Maxwell, A rare haplotype of the vitamin D receptor gene is protective against diabetic nephropathy, *Nephrol. Dial. Transplant.* 25 (2010) 497–503.
- [220] M.J. Taverna, et al., Taq I polymorphism of the vitamin D receptor and risk of severe diabetic retinopathy, *Diabetologia* 45 (2002) 436–442.
- [221] M. Pani, J. Seissler, K. Usadel, K. Badenhop, Vitamin D receptor genotype is associated with Addison's disease, *Eur. J. Endocrinol.* 147 (2002) 635–640.
- [222] M. Fichna, et al., Association of the CYP27B1 C(–1260)A polymorphism with autoimmune Addison's disease, *Exp. Clin. Endocrinol. Diabetes* 118 (2009) 544–549.
- [223] Ö. Ates, Analysis of vitamin D receptor (VDR) gene polymorphisms in Alopecia Areata, *J. Clin. Anal. Med.* 8 (2017) 151–154.
- [224] A. Latini, et al., VDR polymorphisms in autoimmune connective tissue diseases: Focus on Italian population, *J. Immunol. Res.* 2021 (2021) 1–6.
- [225] B. Bugaj, J. Wielińska, J. Świerkot, K. Bogunia-Kubik, K. Górna, VDR polymorphic variants are related to Improvements in CRP and disease activity in patients with Axial Spondyloarthritis that Undergo Anti-TNF treatment, *Genes* 13 (2022) 1873.
- [226] K. Mårdild, et al., Maternal and neonatal vitamin D status, genotype and childhood celiac disease, *PLoS One* 12 (2017) e0179080.
- [227] J.I.S.- Pedro, et al., Heterogeneity of vitamin D receptor gene association with celiac disease and type 1 diabetes mellitus, *Autoimmunity* 38 (2005) 439–444.
- [228] E. Ramos-Lopez, et al., Vitamin D receptor polymorphisms are associated with Graves' disease in German and Polish but not in Serbian patients, *Thyroid* 15 (2005) 1125–1130.
- [229] M.A. Pani, A polymorphism within the vitamin D-binding protein gene is associated with Graves' disease but not with Hashimoto's thyroiditis, *J. Clin. Endocrinol. Metab.* 87 (2002) 2564–2567.
- [230] J. Djurovic, et al., Association between FokI , ApaI and TaqI RFLP polymorphisms in VDR gene and Hashimoto's thyroiditis: preliminary data from female patients in Serbia, *Int. J. Immunogenet.* 42 (2015) 190–194.
- [231] H.W.Z. Hanna, et al., Vitamin D status in Hashimoto's thyroiditis and its association with vitamin D receptor genetic variants, *J. Steroid Biochem. Mol. Biol.* 212 (2021) 105922.
- [232] S. Yesil, et al., Vitamin D receptor polymorphisms in immune thrombocytopenic purpura, *Pediatr. Int.* 59 (2017) 682–685.

- [233] J.J. Eloranta, et al., Association of a common vitamin D-binding protein polymorphism with inflammatory bowel disease, *Pharmacogenet. Genomics* 21 (2011) 559–564.
- [234] F. Marini, et al., Study of vitamin D status and vitamin D receptor polymorphisms in a cohort of Italian patients with juvenile idiopathic arthritis, *Sci. Rep.* 10 (2020) 17550.
- [235] A. Maalej, et al., Association study of VDR gene with rheumatoid arthritis in the French population, *Genes Immun* 6 (2005) 707–711.
- [236] S. Yoshida, et al., A GC polymorphism associated with serum 25-hydroxyvitamin D level is a risk factor for hip fracture in Japanese patients with rheumatoid arthritis: 10-year follow-up of the Institute of Rheumatology, Rheumatoid Arthritis cohort study, *Arthritis Res. Ther.* 16 (2014) R75.
- [237] M. Despotović, et al., Association of vitamin D receptor genetic variants with bone mineral density and inflammatory markers in rheumatoid arthritis, *Clin. Biochem.* 87 (2021) 26–31.
- [238] M. Brink, et al., Vitamin D in individuals before onset of rheumatoid arthritis - relation to vitamin D binding protein and its associated genetic variants, *BMC Rheumatol* 2 (2018) 26.
- [239] E. Puncėviciene, et al., Vitamin D and VDR gene polymorphisms' association with rheumatoid arthritis in Lithuanian population, *Medicina (B. Aires)*. 57 (2021) 346.
- [240] Y.M. Hussien, et al., Polymorphism in vitamin D receptor and osteoprotegerin genes in Egyptian rheumatoid arthritis patients with and without osteoporosis, *Mol. Biol. Rep.* 40 (2013) 3675–3680.
- [241] S. Sobeih, et al., Evaluation of the correlation between serum levels of vitamin D and vitamin D receptor gene polymorphisms in an Egyptian population, *Int. J. Dermatol.* 55 (2016) 1329–1335.