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Genetic and Biochemical Factors Related to the Risk and Disability Progression in Multiple Sclerosis

Daniel Čierny, Jozef Michalik, Ema Kantorová,
Egon Kurča and Ján Lehotský

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Abstract

Sclerosis multiplex (multiple sclerosis, MS) is a chronic autoimmune inflammatory disease of the central nervous system. The immune regulatory defects lead to the process of inflammation and neurodegeneration that results in the deterioration of neurological functions. It is still unclear as to why MS is so devastating and rapidly progressive in one patient and less so in another. It is known that the etiopathogenesis of MS is very complex, and many factors can be involved in the risk and character of the disease and its progression. In this chapter, we discuss the general molecular and cellular mechanisms of action of genetic and biochemical factors that are related to immune system regulation and thus can be connected to the individually varying risk and disability progression of MS. We found that gene variants of the gene polymorphism rs6897932 in interleukin 7 receptor α chain gene rs10735810 in vitamin D receptor gene and *HLA-DR* and *HLA-DQ* genes as well as the serum level of vitamin D are associated with MS risk or disability progression in Central European Slovak population.

Keywords: multiple sclerosis, risk, disability progression, gene polymorphism, biochemical marker

1. Introduction

In triggering an autoimmune response in multiple sclerosis (MS), environmental factors have a strong effect and interact with complex risk-conferring genetic variants [1–3]. In this process, the myelin reactive T cells with altered functional characteristics are formed and

activated [4]. The immune regulatory defects and increased migration of autoreactive lymphocytes within the brain, that are the typical traits in MS, lead to the process of inflammation, myelin sheath breakdown, demyelination, remyelination, neuronal and axonal degeneration, and subsequent deterioration of neurological functions [5]. Neurodegeneration, neuronal and axonal damage that correlate with the progression of the disease can be a process partly independent from inflammation and demyelination or even can be the cause of demyelination occurring from the disease onset. Axonal damage in MS is a result of many pathological processes [6, 7].

It is still unclear as to why MS is so devastating and rapidly progressive in one patient and less so in another. Because the etiopathogenesis of MS is very complex, disease development as well as the characteristics of disease progression is probably the consequence of multifactorial interaction. Our work is dedicated to genetic and biochemical markers that were chosen according to their possible role in the modulation of the immune response in MS patients and thus could be associated with MS risk and disability progression. In our work, we discuss the immune response-related genetic factors associated with MS that can be generally classified into *HLA* genes and *non-HLA* genes. Since vitamin D can have an important role in the pathogenesis of MS, great part of our work is dedicated to its metabolism, functions, mechanisms of action in MS and genetic factors that can modify these effects. In this work, we also present the results of our own analysis of genetic and biochemical markers that we found to be associated with MS risk or progression in the group consisting of MS patients with clinically diagnosed MS and healthy individuals from the region of Central Slovakia. To evaluate the disease progression rate, we used the widely accepted multiple sclerosis severity score (MSSS, score range 0.01–9.99) [8] that considers the neurological impairment of the functional systems (expanded disability status scale score) [9] together with disease duration. For the purpose of the association analysis of these markers with the rate of disease disability progression, we stratified MS patients by MSSS scores to three groups—slowly progressing MS (MSSS < 3), mid-rate progressing MS (MSSS 3–6) and rapidly progressing MS (MSSS > 6) [10].

2. Immune response-related genetic factors in the risk and progression of multiple sclerosis

MS is a typical gender-dependent disease; a higher risk of MS is observed in women than in men in all populations and races. A study conducted in Canada found female to male ratio in individuals affected by MS to be 3:1 [11]. The risk of MS development in siblings of an affected individual is estimated to be 5%, in children 2%, in monozygotic twins 25% [5]. However, it has been shown that genetic predisposition is not strong enough to induce disease development, and appropriate environmental triggers are necessary to start the disease process [1, 12]. In general, the MS-associated genes can be classified into genes of the HLA-complex and *non-HLA* genes [3].

3. Gene polymorphisms and haplotypes in the aetiology of multiple sclerosis

The single-nucleotide polymorphism (SNP) is a variation of a single nucleotide, which is present in the population in a frequency higher than 0.01. SNPs are the most common type of genetic variation and are usually caused by somatic or gametic mutations. Nucleotide change can cause the formation or loss of restriction sites for bacterial endonucleases that are able to cleave the specific DNA sequence. The identification of gene polymorphisms that are in correlation with other risk factors, including biochemical markers, can be useful in establishing the risk of MS development, prognosis, clinical course of the disease and response to therapy. Haplotype (haploid genotype) is a certain combination of alleles or SNPs in the sequence of the DNA, which is localized on one chromosome and is inherited together. When two alleles are in linkage disequilibrium, they are inherited together in a higher frequency than expected randomly [13]. The combination of more alleles, known as tagging SNPs, enables us to identify the other associated alleles. For example, the allele A of gene polymorphism rs3135388 corresponds to the incidence of allele HLA-DRB1*1501, which is the most common genetic risk factor for MS development [14–16].

4. HLA genes and MS

Antigen expression that is inducible by cytokines is different on the various immune cells. Major histocompatibility complex II (MHCII) antigens are transmembrane proteins localized on the immune cells, thus having an important role in the process of exogenous antigen presentation to T cells. MHCII molecules are coded by the gene of human leucocyte antigens D (*HLA-D* gene) that is localized on chromosome 6 and has three regions—HLA-DP, HLA-DQ and HLA-DR [17]. The susceptibility of the population to autoimmune diseases depends on the individual ability to express HLA-DQ and HLA-DR antigens. This expression can be induced by virus infection, most likely by EBV, influenza or paramyxovirus [18]. *MHCII* gene expression is regulated by vitamin D through its binding to the *vitamin D-responsive elements* (VDREs) that are localized in the promoter region of *HLA-DRB1* gene. This fact can explain the interaction between vitamin D, that is an important factor modifying MS development and disease course, and genetic predisposition to MS represented mainly by a highly conservative allele HLA-DRB1*1501. HLA-DRB1*1501 allele is in general considered to be the most important susceptibility allele of MS [19–24]. This allele was found to be present in over 50% of MS cases [25, 26]. The increased frequencies of the DRB1*15 allele in MS patients have been described in Northern Europeans [23, 27], South and North Americans [20, 28], Mediterraneans [29, 30] and African Americans [21]. In Spanish cohorts, the DRB1*03 was the second most frequent allele associated with MS, but only after eliminating HLA-DRB1*15 [29]. The DRB1*03 allele has also been found to be significantly associated with the increased risk of MS in Scandinavians [27], Sardinians [31], and Australians [32]. Fernández et al. [33] found that the DRB1*13 allele is protective against MS development in Spaniards. A protective effect of the alleles DRB1*01, DRB1*07, DRB1*12 and DRB1*14 was confirmed in the recent meta-

analysis in Caucasians [24]. The allele DRB1*07 was found to be protective against MS also in Scandinavians [34]. The DRB1*13.03 allele was found to be the primary risk allele in MS patients of European descent [23]. The protective effect against MS has also been shown for the HLA-DRB1*11 allele [24, 29].

The DQB1*06:02 allele was found to be linked to the increased risk of MS with a proved tight linkage disequilibrium between DRB1*15 and DQB1*06 in Caucasians [35]. As the risk factor of MS, DQB1*06:02 allele has also been identified in a cohort of Afro-Brazilians [36] and Spaniards [33]. Kaushansky et al. [37] suggested that the role of the DRB1*15:01 and DQB1*06:02 alleles in MS depends on the heterogeneous interaction of target antigen, genotype, and phenotype. On the contrary, Isobe et al. [38] found none of the HLA-DQB1 alleles to be associated with MS in African Americans. According to the combinations of HLA-alleles, the association of HLA-DRB1*15/*15 genotype with MS was identified by several studies [32, 34, 39]. In multi-case MS families, Barcellos et al. [39] identified a high risk DRB1*15/*08 genotype and protective DRB1*15/*14 genotype. The study of Sawcer et al. [23] indicates that in all populations of North-European ancestry, a predisposition to MS is linked with the DRB1*15:01-DQB1*06:02 haplotype. Furthermore, Link et al. [34] in a Scandinavian cohort showed that risk haplotypes for MS are almost all DRB1*15 bearing haplotypes, while protective effect against MS development are HLA class I A*02 allele-bearing haplotypes. In Sardinian MS patients, Cocco et al. [40] confirmed a positive association of the haplotype HLA DRB1*03:01-DQB1*02:01 with MS.

In the study from our laboratory, we analysed the association of the *HLA-DRB1/DQB1* genes, alleles and their combinations with susceptibility to MS in the population from central Slovakia. We found that the increased risk of MS is in individuals carrying alleles HLA-DRB1*15, DRB1*03 and DQB1*06, genotypes HLA-DRB1*15/*15 DQB1*06/*06 and haplotype DRB1*15-DQB1*06. In addition, we also found that HLA-DRB1/DQB1 class II alleles DRB1*07, DRB1*13, DQB1*03, genotypes DRB1*13/*11, DQB1*05/*03 and haplotypes DRB1*13-DQB1*06 and DRB1*11-DQB1*03 are associated with the protection against MS development. We cannot exclude that the proposed protective effects of the DRB1*11-DQB1*03 and DRB1*13-DQB1*06 haplotypes in our cohort could be, at least partially, due to the linkage disequilibrium with alleles in the HLA class I region which is primarily associated with MS [41].

5. *Non-HLA* genes and MS

Gene products of *non-HLA* genes can contribute to the genetic risk of MS by modulation of different processes. These genes are involved in the regulation of functions of T- and Bcells, dendritic cells, NKcells, cytokine signalization, metabolism of interferons, vitamin D metabolism, neuronal regeneration and many others [3]. It has been found that these genes can contribute not only to the increased inherited risk of MS development but also to the risk of other autoimmune diseases [42, 43]. The examples of the SNPs involved in the etiopathogenesis of MS are summarised in **Table 1**.

<i>Gene</i>	<i>function</i>	<i>Localization</i>	<i>SNP</i>	<i>Alleles</i>
<i>HLA-DRB1*1501</i> (human leucocyte antigen <i>DRB1*1501</i>)	Antigen presentation	6p21	rs3135388 rs3135005	C/T C/T
<i>IL-7Ra</i> (<i>interleukin 7 receptor receptor alpha chain</i>)	Proliferation of memory Tcells, T- and B-cell development	5p13	rs6897932	C/T
<i>IL-2Ra</i> (<i>interleukin 2 receptor receptor alpha chain</i>)	Sensitization of Tcells to IL-2, proliferation of Tcells	10p15	rs2104286 rs12722489 rs11256369 rs7076103	A/G A/G C/G C/T
<i>CD58</i> (<i>cluster of differentiation 58</i>)	Function of regulatory Tcells	1p13	rs2300747 rs6677309 rs12044852	A/G A/C A/C
<i>CD6</i> (<i>cluster of differentiation 6</i>)	Regulation, adhesion of T _{H17} and other Tcells	11q13	rs17824933 rs12288280	C/G G/T
<i>CLEC16A</i> (<i>C-type lectin domain family 16 member A</i>)	Cell receptor, induction of immune response	16p13	rs6498169 rs12708716	A/G A/G
<i>VAV1</i> (<i>vav guanine nucleotide exchange factor 1</i>)	Lymphocyte survival, differentiation and proliferation	19p13	rs2546133 rs2617822	C/T A/G
<i>PRKCA</i> (<i>protein kinase C alpha</i>)	Regulation of IL-2 expression, receptor	17q22-q23	Allele variants in introns 3, 8	
<i>EVI 5</i> (<i>ecotropic viral integration site 5 protein homolog</i>)	Nuclear protein, cell cycle regulation	1p22	rs6680578 rs11808092 rs11804321	A/T A/C C/T
<i>IRF5</i> (<i>interferon regulatory factor 5</i>)	Regulation of cytokine activation	7q32	rs4728142 rs3807306	A/G A/C
<i>IRF8</i> (<i>interferon regulatory factor8</i>)	Expression of interferon response genes, development of Bcells	16q24	rs17445836	A/G
<i>TYK2</i> (<i>tyrosin kinase 2</i>)	Gene expression	19p13	rs34536443 rs55762744	C/G C/T
<i>TNFRSF1A</i> (<i>tumour necrosis factor receptor superfamily member 1A</i>)	Receptor for tumour necrosis factor	12p13	rs1800693 rs4149584 rs767455 rs4149577	A/G A/C/G C/T C/T
<i>CD40</i> (<i>cluster of differentiation 40</i>)	Receptor for tumour necrosis factor	20q12-q13	rs1883832	C/T
<i>CD226</i> (<i>cluster of differentiation 226</i>)	Activator of NKcells, lymphocyte adhesion, co-stimulator of Tcells	18q22	rs763361	C/T
<i>KIF1B</i> (<i>kinesin family member 1B</i>) <i>kinesin family member 1B</i>)	Neuronal regeneration	1p36	rs10492972	C/T
<i>GPC 5</i> (<i>glypicane 5</i>)	Neuronal growth and reparation	13q32	rs9523762	A/G

Table 1. Gene polymorphisms involved in the etiopathogenesis of MS [3, 44–48].

6. Genetic variants in *interleukin 7 receptor α chain (IL-7Ra) gene*

IL7 is a type 1 short-chain cytokine of the haematopoietin family involved in the modulation of T- and B-cell development and T-cell homeostasis. To perform the immune system functions, IL7 binds to the transmembrane receptor that is formed by heterodimerising the common cytokine gamma chain and IL7 receptor alpha chain (IL7Ra or CD127). IL7Ra is a membrane glycoprotein folded to bind and mediate the action of IL7 and other alpha helical cytokines. IL7Ra consists of an extracellular domain, transmembrane region and cytoplasmic tail, which uses kinases for signal transduction [49]. The localization of the *IL7Ra* gene is chromosome 5p13.3. An increased expression of IL7Ra in peripheral blood mononuclear cells was found in MS patients when compared to controls [50, 51]. The IL7Ra and IL7 mRNA increased expression was found also in the cerebrospinal fluid of MS patients, possibly suggesting an altered balance between the isoforms of IL7Ra and a higher signal-inducing immune cell proliferation and survival [52]. According to the alternative splicing of exon 6 in *IL7Ra* gene, membrane-bound or soluble isoforms of IL-7Ra are produced [53]. A significantly increased ratio of the membrane-bound to soluble isoforms of IL7Ra in MS patients can facilitate the aberrant activation of potentially auto-reactive T cells [54].

Single-nucleotide polymorphisms in *IL7Ra* gene are involved in the dysregulation of immune homeostasis and thus can be associated with susceptibility to MS [55]. A genome-wide study in a large group of subjects from the UK and USA identified the strong association between SNP rs6897932 in *IL7Ra* gene and the risk of MS [2]. The non-conservative amino acid change on position 244 (Ile → Thr) of IL7Ra is a result of the SNP rs6897932 (ATC → ACC) in exon 6 of *IL7Ra* gene [56]. This amino acid change has a functional effect on the product of expression of alternative spliced *IL7Ra* gene, which is manifested by changes in the proportion of the soluble versus membrane-bound isoforms of IL7Ra. The change of this ratio can be followed by a different regulation of the IL7 signal transduction pathway and directly associates the SNP rs6897932 with MS [57].

It has been found that allele C of SNP rs6897932 in *IL7Ra* gene contributes to the increased genetic risk of MS in groups of MS patients from the USA [57, 58], South Spain [59], Nordic countries—Denmark, Finland, Norway and Sweden [52], France [60], Netherlands [61] and Japan [62]. The homozygosity for C allele was identified as a risk genotype for MS susceptibility in Netherlands [61] and Spain [59]. A genotype association was also confirmed by the finding of increased counts of CC genotype of rs6897932 in MS patients compared to controls in the cohorts from the USA [58] and Japan [62]. Corresponding with the contribution of allele C to the risk of MS, the protective effect of allele T for MS risk in a Nordic case-control group has been reported by Lundmark et al. [52]. The protective effect of allele T has been reported also in Spain by Alcina et al. [59]. On the contrary, no association between SNP rs6897932 and MS was found in cohorts of MS patients from Northern Ireland [58], Germany [44] and Western Balkan countries—Serbia, Croatia and Slovenia [63].

Only a few studies addressed the question whether the rs6897932 in *IL7Ra* gene contributes only to the genetic risk of MS, or whether it can also affect the disease course and disability progression [44, 57, 61, 64]. Groups of patients with different forms of MS were compared in

several studies. In Northern European primary-progressive MS cases (PP MS), the underexpression of *IL7Ra* gene as well as different allele frequencies of *IL7Ra* promoter SNP was confirmed. Moreover, *IL7Ra* gene expression was found to be up-regulated in secondary-progressive MS (SP MS) patients [64]. In a study by Akkad et al. [44] in German MS patients, it was found that the soluble *IL7Ra* reduced the expression and allelic and genotypic association between rs6897932 and SP or PP MS but not with RR MS. In their study, a significantly higher frequency of allele C and genotype CC of rs6897932 in SP and PP MS patients was found, but not in RR MS patients compared to controls. The assessment of the severity of MS by MSSS did not show any association between rs6897932 genotype and disease severity in the USA [57]. Differences in allele frequencies in SP MS patients compared to healthy controls were reported in Dutch MS patients by Sombekke et al. [61]. In spite of that, no association between rs6897932 genotype and disease severity (MSSS, EDSS, other clinical tests) and disease activity (relapse rate and MRI markers) was found.

Results of our own work suggest the relevance of rs6897932 allele and gene variants in MS pathogenesis in Slovaks [10]. Our results have revealed that allele C is present in a higher frequency in MS patients (77.4%) as compared to the control group (72.3%), which indicates an increased risk of MS development (OR=1.314, 95% CI=1.004–1.720, $p=0.047$). Interestingly, allele T was manifested in MS patients in a significantly lower frequency representing only 22.6% as compared to 27.7% in controls. This suggests that allele T seems to be protective against MS development (OR = 0.761, 95% CI = 0.582–0.996, $p = 0.047$). The additive model fitted the best to assess association between genotypes and MS risk. Logistic regression analysis adjusted for sex and age revealed that there is a significant association between *IL7Ra* rs6897932 genotype and MS risk (OR = 0.764, 95% CI = 0.586–0.995, $p_{\log} = 0.045$). The genotype analysis showed that MS patients manifested a lower frequency of genotype CT when compared to controls (34.8% vs. 36.3) and genotype TT (5.2% vs. 9.9%) and a higher frequency of genotype CC (60.0% vs. 54.1%). When we used the additive genetic model, we found a significantly decreased risk of MS development in carriers of allele T with genotype CT (OR = 0.865, 95% CI = 0.609–1.228, $p = 0.05$) as well as with genotype TT (OR = 0.565, 95% CI = 0.282–1.132, $p = 0.05$).

After stratification of MS patients according to the disease disability progression rate, we found a significantly lower frequency of allele T in the subgroup of rapidly progressing MS patients (18.1%) as compared to 27.7% in controls. These results suggest that allele T is associated with protection against rapid disability progression of MS (OR = 0.576, 95% CI = 0.348–0.955, $p = 0.031$). An additive genetic model adjusted for sex and age fitted the best to assess the association between genotypes and the rate of disease disability progression. Linear logistic regression with disease disability rate as the dependent variable—MSSS (1, 2, 3 and 0 for controls) revealed that there is a significant association between *IL7Ra* rs6897932 genotype and disability progression of MS ($p_{\log} = 0.034$). Genotype analysis showed that the frequency of genotype TT is higher in controls (9.6%) and lower in MS patients with rapid disability progression (3.5%). Frequency of genotype CC was higher in rapidly progressing MS patients (67.2%) and lower in controls (54.1%). The data suggest that individuals carrying genotype TT are protected against rapid disease disability progression of MS.

We have shown for the first time in a Central European Slovak population that allele C of rs6897932 is associated with the risk of MS, and allele T has a protective additive effect against MS susceptibility. Moreover, we revealed that minor allele T and genotype TT of rs6897932 in the *IL7Ra* gene are protective against rapid disease disability progression in MS [65].

7. Vitamin D and its role in risk and progression of multiple sclerosis

In the past decades, much attention has been given to vitamin D and its role in MS and other autoimmune diseases. The following sections are dedicated to the metabolism and structure of vitamin D, its immunological effects, serum level and mechanisms of action of vitamin D in the prevention and treatment of MS. We also describe the genetic factors that can modulate the biological effects of vitamin D.

7.1. The structure and metabolism of vitamin D

Vitamin D in the human body undergoes a complex metabolism. Cholecalciferol (vitamin D₃), as a precursor of a hormonally active form, is produced in the skin from 7-dehydrocholesterol after sunlight exposure and can also be absorbed from the diet. Subsequently, cholecalciferol is hydroxylated in the liver forming 25-hydroxycholecalciferol, calcidiol. The hormonally active form of vitamin D, 1,25-dihydroxycholecalciferol, calcitriol, is produced by further hydroxylation especially in the kidneys and also in other tissues. The enzyme catalysing this hydroxylation is 25-hydroxyvitamin D-1 α -hydroxylase, coded by *CYP27B1* (cytochrome P450 family 27 subfamily B member 1) gene [66, 67]. In various cells, the bioactive form of vitamin D binds to the vitamin D receptor (VDR) providing its physiological functions by modulation of the target gene's transcription [68]. The circulating serum level of vitamin D depends not only on environmental factors such as exposition to sunlight and vitamin D intake but also on genetic and epigenetic factors. The genetic factors can influence the effects of vitamin D through the variability of the genes participating in its activation and degradation, transport and receptor signalling [69].

7.2. The effect of vitamin D on the functions of immune cells

There is growing evidence that vitamin D not only regulates bone metabolism but also has large-scale immunomodulatory and anti-inflammatory effects. A linkage has been found between vitamin D deficiency and increased risk of autoimmune diseases [70]. The immunocompetent cells—macrophages, dendritic cells, T cells and B cells are able to produce calcitriol and express the VDR at the high rate. Through this, vitamin D modulates the synthesis of various cytokines and immunoglobulins and is involved in the regulation of innate and adaptive immune response. Autocrine and paracrine effects of vitamin D depend also on its serum level, and individuals with hypovitaminosis D are in a state of immune system dysfunction and are predisposed to the development of autoimmune diseases [71].

In T cells, calcitriol inhibits the production of IL-12 and IFN- γ and subsequent differentiation of T_{H1} lymphocytes that are the key cells involved in the MS development. Calcitriol improves

the immunosuppressive functions of T_{REG} cells and ameliorates the T_{H2}-cell development by the activation of the promoter region of *IL-4* gene [19, 72]. Vitamin D increases the expression of IL-4, IL-5 and IL-10 that are able to activate T_{H2} cells, decreases the production of IFN- γ , blocks the formation of T_{H1} cells after antigen stimulation and has positive effects on the T_{H1}-mediated autoimmune diseases [73, 74]. B cells, which also participate in the demyelinating process and produce intrathecal immunoglobulins, express VDR and vitamin D hydroxylases. In B cells, calcitriol reduces the intracellular signal pathways of nuclear transcription factor NF-kappa B (NF-kB) and CD40 signalling [75]. Calcitriol inhibits the maturation and proliferation of B cells, induces apoptosis of B cells, inhibits the differentiation of plasma and memory cells and decreases the production of immunoglobulins IgG and IgM [76]. Immature B cells are more prone to regulation by calcitriol when compared to plasma cells. Calcitriol also decreases the expression of MHCII molecules and co-stimulatory molecules in B cells [19].

Calcitriol formed in macrophages inhibits the immune response by suppressing proliferation of T_{H1}- and T_{H17} cells and promoting the functions of T_{H2}- and T_{REG} cells [71]. Calcitriol inhibits the secretion of IL-12 by antigen-presenting cells and monocytes [77]. Vitamin D blocks the differentiation of immature dendritic cells and the expression of co-stimulatory molecules CD40, CD80, CD86 and MHC II, thus decreasing the capacity of dendritic cells to activate autoreactive T cells. Vitamin D also ameliorates the spontaneous apoptosis of mature dendritic cells [73]. In macrophages, calcitriol suppresses intracellular oxidative burst and listericidal activity. It also suppresses the expression of Fc and TLR receptors induced by IFN- γ that are important for antigen recognition [78]. Vitamin D suppresses the proliferation of antigen-specific T cells and chemotaxis of dendritic cells by decreasing the expression of differentiation antigens CD80, CD86 and HLA-DR molecules [79].

7.3. The murine model of MS and vitamin D

In mice that lack the *VDR* gene or the gene of the enzyme catalysing vitamin D activation, an abnormal development and function of T_{H1}-lymphocytes and deficiency of peripheral T-lymphocytes have been observed [80, 81]. Calcitriol treatment can prevent the induction and progression of autoimmune diseases including experimental autoimmune encephalomyelitis (EAE), a murine model of MS [82, 83]. Calcitriol can also decrease the severity of EAE symptoms, and its deficiency causes an increased susceptibility of animals to EAE induction [77, 82]. In mice with chronic EAE, vitamin D administration suppresses the proliferation of specific T_{H1} cells, inhibits IL-12 dependent production of IFN- γ , prevents relapses and reduces perivascular infiltration, demyelination plaque formation and axonal degeneration in the brain and spinal cord [84].

7.4. Serum level of vitamin D and dose management

To reflect vitamin D status in the human body, calcidiol plasma level measurement is usually used. Calcidiol is the main circulating form of vitamin D in plasma, and its biological half-time is 19 days [85]. The recommended daily dose of vitamin D is approximately 10 times higher than in the past. The optimal serum level of vitamin D is 75–250 nmol/l (30–100 ng/ml). In

countries with less sunny climate, the necessary daily dose of vitamin D is 1000–4000 IU/day ($1 \mu\text{g} = 40 \text{ IU}$) [86].

The risk of vitamin D overdosing is hypercalcaemia and subsequent organ and tissue damage. Whole body exposure to sunlight results in the production of around 10,000 IU of vitamin D, so it is not simple to cause vitamin D intoxication by its short-term peroral supplementation. The results of several studies suggest that even high-dose vitamin D₃ supplementation in MS patients is safe and clinically useful. Burton et al. [87] administered high peroral doses of vitamin D to healthy individuals and MS patients. The initial dose was 40,000 IU/day during 28 weeks, followed by 10,000 IU/day during 12 weeks; later it was gradually decreased to 0 IU/day, combined with 1.2 grams of calcium per day. During the period of 40,000 IU of vitamin D per day, the serum levels reached 413 nmol/l, which was higher than the conventional limit established for vitamin D toxicity (250 nmol/l). Calcidiol serum levels remained around this limit for 18 weeks without any observed negative effects. The serum level of calcium was in the physiological reference range during the whole study duration. Moreover, no cardiac rhythm abnormalities or impairment of hepatic or renal functions was observed. Kimball et al. [88] administered 4000–40,000 IU/day to patients in the active phase of MS together with 1.2 grams of calcium. Medium serum level of calcidiol was $78 \pm 35 \text{ nmol/l}$ and rose to $386 \pm 157 \text{ nmol/l}$. Serum calcium level and urinary calcium to creatinine ratio did not exceed the physiological reference values. Vitamin D supplementation in this study did not cause any change in the serum level of hepatic enzymes, creatinine, electrolytes, proteins and parathormone. Although the serum level of calcidiol doubled the physiological upper range value, hypercalcaemia or hypercalciuria was not observed.

Although the significant toxicity of vitamin D₃ was not observed even in doses of 40,000 IU/day, its daily dose in healthy individuals should not exceed 2000 IU. The optimal daily dose of vitamin D₃ that should be routinely recommended to women during pregnancy and lactation is 1000 IU. Children born in families with MS history should be administered daily 200–400 IU of vitamin D₃ [66].

7.5. Vitamin D and the course, prevention and treatment of MS

The role of vitamin D in the prevention of MS development has been confirmed by many experimental, epidemiological, genetic and immunological studies. Vitamin D insufficiency during the whitematter development can alter the pathways of axonal differentiation and adhesion and increase the apoptosis of oligodendrocytes that express VDR. This results in local microenvironmental changes and altered regenerative and remyelinating capacity [66]. In individuals with an increased genetic risk of MS, it is possible to prevent the demyelination process by preventive vitamin D administration. This preventive strategy would be better than reparation of already developed myelin and axonal damage [12, 66].

High-dose peroral vitamin D intake has been found to be inversely associated with the risk of MS in a cohort of more than 90,000 women. Peroral vitamin D supplementation in a dose higher than 400 IU/day leads to the reduction of MS risk when compared to the individuals with no vitamin D intake ($\text{RR} = 0.59$, $95\% \text{ CI} = 0.38\text{--}0.91$, $p = 0.006$) [89]. Also, calcidiol plasma levels are

inversely correlated with MS risk. This association is particularly obvious in whites, while among blacks and Hispanics with lower 25-hydroxyvitamin D levels than whites, there was no significant association between vitamin D and MS risk [90]. Vitamin D also has reparative effects for the nervous tissue, especially in patients in the early phases of the disease. In countries with low sun exposure, food supplementation of vitamin D could be a simple and cheap method of MS prevention [86]. The incidence of MS could be reduced by the administration of vitamin D to pregnant women, and all children living in mild climates should be more exposed to sunlight and should be on a vitamin D-rich diet [66].

Vitamin D is not only a factor modifying MS risk, but it can also have a role in the modulation of disease course. It has been observed that in relapsing remitting MS, calcidiol plasma levels are lower during relapses compared to the periods of remission [91]. In addition, there is evidence that lower calcidiol levels are associated with higher relapse rates and higher risk of exacerbation, as well as higher expanded disability status scale (EDSS) scores and progressive forms of MS [92–94]. Vitamin D can improve memory and cognitive impairments in patients with MS, Alzheimer disease and in patients after chemotherapeutical treatment [95]. High-dose peroral vitamin D supplementation has immunomodulatory effects and leads to reduction in the number of relapses and suppression of the inflammatory activity and proliferation of Tcells [87], as well as the decrease in the number of gadolinium-enhancing lesions in brain [88].

In our study, we examined the serum levels of calcidiol in a group of MS patients from the Central-Northern part of Slovakia. We found that hypovitaminosis D is more frequent in MS patients, when compared to healthy individuals. Serum levels of calcidiol were significantly lower in MS patients when compared to controls (15.0 ± 6.1 ng/ml vs. 18.2 ± 8.3 ng/ml, $p_{(K-W)} = 0.001$). Moreover, we found that there is an association of the serum level of vitamin D with the rate of MS disability progression ($p_{(K-W)} = 0.000$). We detected similar serum levels of calcidiol in slow progressing and mid-rate progressing MS patients (15.7 ± 5.0 ng/ml vs. 15.8 ± 6.6 ng/ml), but interestingly we noticed a marked decrease of calcidiol serum levels in rapidly progressing MS patients (12.8 ± 5.9 ng/ml). In addition, calcidiol level was significantly lower in all subgroups of MS patients when compared to controls (18.2 ± 8.3 ng/ml). Thus we can conclude that decreased serum level of calcidiol in MS patients can be one of the factors related to increased risk of MS development, as well as increased risk of rapid disease disability progression.

7.6. Genetic factors related to vitamin D effects in MS

Nucleotide exchange in DNA sequence can cause the production of protein products with different activities. Polymorphisms of the genes involved in the activation, transport, signaling and degradation of vitamin D can, together with other factors, modify the individual immune response and thus can be related to MS. Because of the beneficial effects of vitamin D, in individuals with genes predisposing to its higher serum levels, the risk of MS should be reduced [96]. The serum level of vitamin D can be modified by *VDR* gene polymorphisms [97–99]. The fact that serum levels of vitamin D are similar in twins, and especially when they are monozygotic twins, speaks in favour of a genetic regulation. Gene polymorphisms FokI in

VDR gene, rs4646536 and rs703842 in the *CYP27B1* gene and rs10741657 in the *CYP2R1* gene are the significant predictors of calcidiol serum level [99]. Hypovitaminosis D is common in higher latitudes because of the lack of sun exposure [100]. The fact that not all vitamin D-deficient individuals develop MS is probably the result of the complexity of the etiopathogenesis of MS and the interaction of many factors. The positive effects of vitamin D in MS can be dampened for example by the allele HLA-DRB1*15 [96]. In MS patients, it is necessary to find out the link between the genotype and the vitamin D serum level and also the genetic interactions among the genes *CYP27B1*, *VDR* and *HLA* [19]. The gene polymorphisms associated with vitamin D metabolism are summarized in **Table 2**.

<i>Gene</i>	<i>function</i>	<i>Localization</i>	<i>SNP</i>	<i>Allele</i>
<i>CYP27B1</i> (cytochrome P450 family 27 subfamily B member 1, 25-hydroxyvitamin D ₃ 1-alpha-hydroxylase)	Hydroxylation	12q13	rs703842	C/T
			rs10877012	G/C
			rs4646536	C/T
			rs10877015	A/G
			rs118204009	A/G
			rs118204012	A/G
<i>CYP2R1</i> (cytochrome P450 family 2 subfamily R member 1, vitamin D ₃ 25-hydroxylase)	Hydroxylation	11p15	rs10741657	A/G
			rs10500804	G/T
			rs12794714	A/G
			rs118204011	C/T
<i>DBP</i> (vitamin D binding protein)	Transport in plasma	4q12	rs7041	G/T
			rs4588	A/C
<i>VDR</i> (vitamin D receptor)	Receptor	12q13	rs1544410 (BsmI)	A/G (B/b)
			rs7975232 (ApaI)	T/C (A/a)
			rs731236 (TaqI)	T/C (T/t)
			rs10735810 (FokI)	C/T (F/f)
			rs11568820 (Cdx2)	G/A
			rs2254210	A/G
			rs98784	C/T
<i>CYP24A1</i> (cytochrome P450 family 24 subfamily A polypeptide, vitamin D 24-hydroxylase)	Deactivation	20q13	rs2296241	A/G

Table 2. The gene polymorphisms associated with vitamin D metabolism [19, 98, 99, 101].

7.6.1. Genetic variants in vitamin D receptor gene in MS

According to the effects of vitamin D in MS, the molecular mechanisms of vitamin D function should be considered. As mentioned earlier, vitamin D executes its physiological effect via

binding and activation of VDR. Interestingly, the activation of VDR by calcitriol can suppress the induction of EAE, while animals that lack VDR are not protected against EAE [102]. The gene for VDR is located on the 12q13 chromosomal region and consists of 11 exons. Non-coding exons 1A, 1B and 1C are located in the 5' end of the VDR gene, and exons 2–9 encode the structural portion of the VDR protein [103]. VDR sequence is similar to that of the receptors for steroid hormones and hormones of the thyroid gland. VDR is a regulatory transcription factor and consists of highly conservative DNA-binding and ligand-binding domains. The signal pathways associated with the VDR regulate the transcription of genes involved in the regulation of bone metabolism, immune response and cancer [83]. The polymorphisms in the initiation codon of the *VDR* gene can cause the formation of transcription variants coding different proteins [104]. In the *VDR* gene, SNPs ApaI (rs7975232), BsmI (rs1544410), FokI (rs10735810) and TaqI (rs731236) have functional biological effects and are mostly studied in MS as well as in other diseases. These gene polymorphisms can alter mRNA level, its stability and alternative splicing and also the stability of the final gene product, amount of protein isoforms and their interactions [105]. FokI gene polymorphism is located in exon 2 of the *VDR* gene, and its variants result in a change of protein structure. There are two possible allele variants, f (presence of a restriction site for FokI endonuclease) and F (absence of a restriction site for FokI endonuclease). It has been confirmed that the f (T) allele leads to the expression of a VDR protein, which is three amino acids longer (427 amino acids) than the F (C) allele (424 amino acids). The shorter isoform of the receptor is more transcriptionally potent through a more efficient interaction with transcription factor TFIIB [105, 106]. Near the 3' end of the *VDR* gene, we can find the ApaI and BsmI polymorphism in the intron between exon 8 and 9 and TaqI gene polymorphism in exon 9 [107]. The allele variants of these gene polymorphisms and their combinations regulate the functions of VDR through the modulation of mRNA stability. In Caucasians, TaqI, ApaI and BsmI polymorphisms are in strong linkage disequilibrium and are present in five haplotype blocks. Haplotype2 (t-A-B) probably results in a lower number of 'A' in polyA variable number of tandem repeats (VNTR), while haplotype 1 (T-A-b) is connected to a large number of 'A', thus modulating mRNA stability [106]. Morrison et al. [108] found that allele b (G) of the BsmI polymorphism causes a decreased expression of VDR mRNA.

Interestingly, several studies have found an association between *VDR* gene polymorphisms and the risk of MS. Differences in allele frequency of the BsmI polymorphism in the *VDR* gene were found in Japan by Fukazawa et al. [109], who for the first time pointed out the involvement of *VDR* gene polymorphisms in the pathogenesis of MS. The association of *VDR* gene polymorphisms with MS has been confirmed in cohorts of MS patients from Japan [110], the UK [111, 112], Australia [107] and the USA [98]. On the contrary, no association of *VDR* gene polymorphisms with the risk of MS was found by studies in MS patients from Canada [113], Netherlands [114], Greece [115], Spain [116, 117], Tasmania [118] and Iran [119]. The presence of specific haplotypes of the *VDR* gene can increase the risk of MS development, especially its progressive forms. Tajouri et al. [107] in Australia found haplotype A-t (T-C) of ApaI and TaqI polymorphism to increase the risk of MS development, especially its progressive forms. The carriership of allele t (C) in their study increased MS risk twice. Fukazawa et al. [109] found allele b (G) and genotype bb (GG) of BsmI polymorphism to increase MS risk, but without any

association with the form and severity of MS (EDSS, magnetic resonance imaging (MRI)). Allele b (G) of BsmI polymorphism of VDR has been found to be associated with MS risk in combination with allele A (T) of ApaI polymorphism by Niino et al. [110]. However, in their study, they did not find any association of ApaI gene polymorphism with clinical form and severity of MS evaluated by the EDSS score, disease duration and MRI findings. Agliardi et al. [120] in Italy found that allele T (T) and genotype TT (TT) are protective against MS development, supported by the finding that the expression of VDR mRNA is increased four times by genotype Tt (TC) and eight times by genotype TT (TT) when compared to genotype tt (CC). The observed effect is present especially when the protective allele T is present in the combination with HLA-DRB1*15 allele.

The role of VDR gene polymorphisms is still not completely understood, and it seems to vary among different populations. For proper cell signalling to decrease the risk of MS, it is probably necessary to reach a certain level of the transcriptional activity of VDR that is also modified genetically. For proper immunoregulation, the individuals that have the genotype causing the decreased VDR protein activity can need a higher peroral vitamin D intake or higher level of sun exposure. Contrarily, in individuals with higher transcriptional activity of VDR, a lower sun exposure or vitamin D intake can be sufficient for proper immune system regulation.

The findings of our previous study in MS patients from the Central-Northern region of Slovakia have confirmed the association of FokI heterozygous genotype Ff with an increased risk of MS in women [10]. Although we found no statistically significant differences in the proportions of FokI genotypes or allele frequencies between total MS patient and the control group, we have observed significant differences in the FokI genotype distribution between women with MS and the female control group ($p = 0.042$). Our results have shown a significantly higher frequency of heterozygous Ff genotypes in FokI polymorphism in the female MS group (53.4%) as compared to 43.7% in the female control group (OR = 1.48, 95% CI = 1.01–2.16). In spite of this fact, when we compared the subgroup of rapidly progressing MS patients with the subgroup of slow progressing MS patients, allele and genotype counts were not significantly different between them (allele f: 34.5 vs. 43.3%, allele F: 65.5 vs. 56.7%, genotype ff: 10.3 vs. 13.4%, genotype Ff: 48.3 vs. 59.8%). Since we have not shown any significant association between FokI VDR gene polymorphism and the rate of disease disability progression in our cohort of Slovak MS patients, we observed a trend of higher frequency of homozygotes FF to be 41.4% in MS patients with rapid progression of disease as compared to 26.8% in slow progressing MS patients (OR = 1.93, 95% CI=0.94–3.94) with a marginal level of significance ($p = 0.071$). From the results of our study, it seems that contributions from genetic and allelic variants of FokI VDR gene polymorphism have only a small impact in a disease as complex as MS, and its role in the etiopathogenesis of MS still remains controversial.

8. Conclusions

In summary, we can conclude that many genetic and biochemical factors can be involved in the etiopathogenesis of MS. These markers could be used to evaluate the risk of MS development and the risk of rapid disease disability progression.

The proposed markers that have been found to be associated with MS risk or disability progression in Central European Slovak population are summarized in **Table 3**. In our studies, we identified decreased serum level of vitamin D, allele C and genotype CC of polymorphism rs6897932 in the *IL7Ra* gene, genotype Ff of rs10735810 in the *VDR* gene (only in women); HLA-alleles DRB1*15, DRB1*03, DQB1*06; HLA-genotypes DRB1*15/*15, DQB1*06/*06 and HLA-haplotype DRB1*15-DQB1*06 as the main risk factors for MS development. On the contrary, allele T of rs6897932 in the *IL7Ra* gene (in individuals with genotype CT and TT); HLA-alleles DRB1*07, DRB1*13, DQB1*03; HLA-genotypes DRB1*13/*11, DQB1*05/*03 and HLA-haplotypes DRB1*13-DQB1*06 and DRB1*11-DQB1*03 displayed a protective effect against MS development. Genotype CC of rs6897932 in the *IL7Ra* gene and decreased serum level of vitamin D were identified as negative prognostic factors for rapid disability progression in MS, while minor allele T of rs6897932 in the *IL7Ra* gene (especially in individuals with TT genotype) was identified as a protective factor disability progression.

	<i>MS development</i>	<i>Rapid disease disability progression</i>
Risk factors	Decreased serum vitamin D rs6897932 in <i>IL7Ra</i> gene—allele C, genotype CC HLA-alleles DRB1*15, DRB1*03, DQB1*06; HLA-genotypes DRB1*15/*15, DQB1*06/*06; HLA-haplotype DRB1*15-DQB1*06 rs10735810 in <i>VDR</i> gene —genotype Ff (only women)	Decreased serum vitamin D rs6897932 in <i>IL7Ra</i> gene—genotype CC
Protective factors	rs6897932 in <i>IL7Ra</i> gene—allele T, genotype CT and TT HLA-alleles DRB1*07, DRB1*13, DQB1*03; HLA-genotypes DRB1*13/*11, DQB1*05/*03; HLA-haplotypes DRB1*13-DQB1*06, DRB1*11- DQB1*03	rs6897932 in <i>IL7Ra</i> gene—allele T, genotype TT

Table 3. The proposed markers associated with the MS risk or disability progression in Slovaks [10, 41, 65].

From the results of our study, we conclude that rs6897932 of the *IL7Ra* gene, rs10735810 in the *VDR* gene, HLA-DR and DQ genotypes, as well as serum level of vitamin D may be the important markers that could be used as part of a panel of markers to evaluate the risk of MS development and disability progression. The relevance of these markers identified in our study should be verified in larger groups of individuals not only in Slovakia but also in other different populations. The relevant positive or negative prognostic genetic or biochemical markers can

improve the diagnostic and therapeutic procedure and can help to minimize neurological damage in predisposed individuals.

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Author details

Daniel Čierny¹, Jozef Michalik², Ema Kantorová², Egon Kurča² and Ján Lehotský^{3*}

*Address all correspondence to: lehotsky@jfmed.uniba.sk

1 Department of Clinical Biochemistry, Jessenius Faculty of Medicine and University Hospital Martin, Comenius University in Bratislava, Martin, Slovak Republic

2 Department of Neurology, Jessenius Faculty of Medicine and University Hospital Martin, Comenius University in Bratislava, Martin, Slovak Republic

3 Department of Medical Biochemistry and BioMed, Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava, Martin, Slovak Republic

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