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ORIGINAL ARTICLE

Association of Vitamin D Receptor, Interleukin7 Receptor Alpha Gene Polymorphisms With The Risk Of Multiple Sclerosis

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ABSTRACT

Background: Multiple sclerosis (MS) is a chronic autoimmune neurodegenerative disease with unknown definite etiology. Many factors have taken part in explanation of MS pathology including genetics and environmental factors. In this study we investigated the frequency of vitamin D receptor (VDR) gene (bsm1 and taq1) and interleukin 7 receptor alpha (IL7RA) gene single nucleotide polymorphisms (SNPs) and their association with the risk of MS. **Methods:** a case control study was performed on two groups. MS group with 63 MS patients diagnosed according to McDonald criteria for MS diagnosis and the control group of 63 apparently healthy individuals not having MS. Blood was collected and DNA was extracted. DNA was amplified using Polymerase chain reaction. Then analysis for VDR SNPs (bsm1 and taq1) by restriction fragment length polymorphism assay. Amplification refractory mutation system technique was carried out to evaluate IL7RA SNP. **Results:** we found that there was statistically significant difference in Bsm1 genotyping between case and control groups (p=0.02). As for IL7RA genotype frequency between MS patients and controls there was statistically significant difference (p=0.004). And lastly Taq1genotyping revealed no statistically significant association with MS (p=0.5). **Conclusion:** we conclude that VDR (Bsm1) and IL7RA SNPs are related to MS pathogenesis while VDR (Taq1) SNP is not a risk factor for MS in an Egyptian sample.

Key words: Multiple sclerosis, Vitamin D receptor, Interleukin 7 Receptor, gene polymorphism

INTRODUCTION

Multiple sclerosis (MS) is a chronic disease characterized by neuroinflamation and axonal demylination in the central nervous system. The disease usually affects females in reproductive age. Clinically variable neurologic presentations are usually present according to the type of demylinated nerve either: motor sensory or autonomic [1]. In 2015, about 18,900 people died from MS, up

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from 12,000 in 1990[2]. The etiology of MS is unknown. Genetics and environment share in MS pathogenesis. HLA class II haplotype HLA-DRB 1501 was the first identified risk locus to be strongly associated to MS **[3].**Additional 200 non MHC different MS risk loci were further identified[4]. The environmental risk factors for MS include smoking, Epstein–Barr virus (EBV) infection, obesity, vitamin D deficiency, and working night shifts. While oral tobacco, excess coffee drinking, alcohol, and cytomegalovirus (CMV) infection were found to lower the disease risk [5].

In the past decade, much attention has been given to vitamin D and its role in MS. Vitamin D is important for bone and mineral homeostasis and has immunoregulatory and anti-inflammatory functions[6]. Vitamin D mediates its function through vitamin D receptor (VDR) which is expressed on the surface of different immune cells [7]. Many studies on VDR single nucleotide polymorphisms (SNPs) have reported four SNPs of possible disease association; three at the 3' end of the VDR gene (TaqI, BsmI, ApaI) and one at the 5'end (FokI)[8].

Interleukin-7 receptor alpha chain (IL-7Ra) or (CD127) located on chromosome 5P13 was found to be the first non-major histocompatibility complex (non-MHC) susceptibility locus for MS [9]. Interleukin-7 binds the IL7R common gamma chain (namely CD132) and its alpha chain (namely IL7RA or CD127), forming the signaling complex in the IL7 pathway. The IL7/IL7R interaction is essential for the survival, proliferation, and differentiation of T-cells, especially CD4+ T-cells, which is present in the inflammatory lesions of multiple sclerosis patients[10].

METHODS

This is a case control study which included 63 MS patients diagnosed according to McDonald criteria for MS diagnosis and 63 apparently healthy individuals without MS. They didn't have any disease or administrate any drugs that may influence the current study**.** Written informed consent was obtained from all participants and the study was approved by the research ethical committee of Faculty of Medicine, Zagazig University. The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans. Socio-demographic characteristics of the studied groups are shown in **[table 1]**and **[figure 1]**. Clinical data findings of the studied groups are shown in **[table 2]**

Collection of samples:

Peripheral venous blood samples were taken and dispensed into 3 ml tubes containing 5.4 mg of ethylene diamine tetra acetic acid (EDTA) then they were stored at -20°C for DNA extraction.

DNA Extraction

Genomic DNA was extracted from EDTA anticoagulated peripheral blood leucocytes according to the manufacturer's instructions using G-spin™ Total DNA Extraction Mini Kit provided by iNtRON Biotechnology, Korea. Extracted DNA was stored at -20°C for further use.

Purity of DNA could be detected by measuring A260 (the absorbance at 260 nm) to A280 ratio. Pure double stranded DNA sample is assumed to have an A260/ A280 ratio ranging from 1.7 to 1.9. (11)

Detection of VDR (Bsm1 and Taq I) polymorphism by polymerase chain reaction- restriction fragment length polymorphism (PCR-RFLP):

Components of the 20 µl Rxn PCR reaction mixture:

2X PCR Master mix Solution (i-TaqTM) 10 µl
Template DNA 2 µl
Primer (Forward : 10 pmol/ µl) 1 µl
Primer (Reverse : 10 pmol/ µl) 1 µl
Distilled Water 6 µl

Primer sequences (5' to 3'):

1-For Bsm1:

BsmI Forward:
CAACCAAGACTACAAGTACCGCGTCAG TGA
BsmI Reverse:

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AACCAGCGGGAAGAGGTCAAGGG

2- For Taq I:

Taq I Forward:
CAGAGCATGGACAGGGAGCAAG
Taq I Reverse:
GCAACTCCTCATGGCTGAGGTCTCA

PCR Conditioning:

PCR included cycles of: initial denaturation at 94°C for 4 min then 30 cycles of denaturation at 94°C for 30 sec, annealing at 58°C for 30 sec for the BsmI SNP (59°C for 30 sec for the Taq I SNP), extension at 72°C for 1 min, and final extension at 72° C for 5 min. AG Eppendorf. Inc. Mastercycler, Hamburg. Germany was used for amplification reaction.

RFLP was performed using Bsm1 and Taq 1 restriction enzymes purchased from Thermo Fisher Scientific,USA.

The digested PCR products were subjected to gel electrophoresis, stained with ethedium bromide and visualized by UV transilluminator.

The Bsm1 restriction polymorphism showed two possible alleles, allele B and b with three available genotypes: BB, Bb, bb.

DNA yields a single 870 bp band in normal homozygous (BB) with absence of restriction site while in presence of the restriction site two bands (700&170 bp) are obtained in case of bb genotype and three bands (870,700,170 bp) in the heterozygous form (Bb).

The TaqI restriction polymorphism has two possible alleles, allele T and t with three available genotypes: TT, Tt, tt.

Following digestion of the PCR product with TaqI restriction enzyme, 495 and 245 bp fragments appeared in case of homozygous genotype *TT* indicating absence of restriction site, while in presence of the restriction site three fragments (290, 245 and 205 bp) are obtained in case of tt genotype and four fragments (495, 290, 245 and 205 bp) in the heterozygous form (Tt).

Detection of IL7RA gene polymorphism:

Amplification-refractory mutation system (ARMS) was performed to detect IL7RA gene polymorphism.

Four primers were used, two were for internal control and two specific for T or C allele.

The sequence specific forward primer:
5′-AAGAAGGGAAGAGAGCATTGG-3′,
The sequence specific reverse primers were:
5′-GAAAAAACTCAAAATGCTGATGG-3′
(for C allele)
and 5′-AGAAAAAACTCAAAATGCTGATGA-3′
(for T allele)
And the last reverse primer for internal control was:
5′-TTACTTTGGGGACAGCGTTT-3′.

Components of the 20 µl Rxn PCR reaction mixture:

2X PCR Master mix Solution (i-TaqTM) 10 µl
Template DNA 2 µl
Forward Primer 1 µl
Reverse Primer for C allele 1 µl (in case of T allele amplification1 µl of reverse primer for T allele was used instead)
Reverse Primer for internal control 1 µl
Distilled Water 5 µl

PCR Conditioning:

PCR included cycles of: denaturation of 94° C for 5 min followed by 35 cycles of denaturation at 94° C for 30 s, annealing at 62° C for 30 s and extension at 72° C for 30 s. The final extension step was at 72° C for 5 min.

The PCR products were subjected to 1.5 % gel electrophoresis, stained with ethedium bromide and visualized by UV transilluminator.

Statistical analysis

Data were analyzed using SPSS version 23 for data processing..Data were expressed as number and percentage for qualitative variables and mean + standard deviation (SD) for quantitative one. The level of significance was set at *P* value < 0.05.

RESULTS

There was statistically significant difference in Bsm1 genotyping between case and control groups (p=0.02), shown in **[table 3]** and **[figure 2]**. Regarding IL7RA genotype frequency between MS patients and controls, there was statistically significant difference (p=0.004), shown in **[table 5]**. And lastly

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Taq1genotyping revealed no statistically significant association with MS (p=0.5), shown in**[table 4].**

There was a statistically significant difference between MS patients and controls regarding allele frequancies of VDR (BsmI) polymorphism (p=0.01). Inheritance of b allele was associated with nearly 2 fold increase in the risk of MS. In control group, frequency for B allele was 78.6% and frequency for b allele was 21.4%. In MS group, frequency for B allele was 65.1% and frequency for b allele was 34.9%. Chi square (χ^2) was 5.7 and there was a significant association among the studied groups (p=0.01). Odds Ratio (95%CI) was 1.97(1.12-3.45).

There was a a statistically significant difference between MS patients and controls regarding allele frequancies of IL7RA gene polymorphism (p=0.001). Inheritance of T allele was associated with 2.68 fold increase in the risk of MS.

In control group, frequency for C allele was 83,3% and frequency for T allele was 16.7% . In MS group, frequency for C allele was 65.1 % and frequency for T allele was 34.9 %.Chi square (χ^2) was 10.9, p=0.001 and Odd's Ratio (95%CI) was 2.86 (1.48-4.86).

In relation to allele frequency of *VDR (TaqI)* polymorphism, in control group, frequency for T allele was 67.5% and frequency for t allele was 32.5%. In MS group, frequency for T allele was 72.2 % and frequency for t allele was 27.8 %.

Chi square (χ^2) was 0.68 and there was a non significant association among the studied groups regarding allele frequencies of TaqI polymorphism (p=0.41) (>0.05). . Odd's Ratio (95%CI) was 0.79 (0.47-1.37).

Table 1. Comparing socio-demographic characteristics between MS and control groups

Variable	**Case (63) mean ± SD (Range) Median**	**Control (63) mean ± SD (Range) median**	**t-test**	**p-value**
Age	33.1±5.8 (19-44) 34	31.9±4.9 (19-44) 32	1.2	0.2
Variable	**Case No(63) %**	**Control No(63) %**	**χ^2**	**p-value**
Sex			0.04	
Male	15 23.8%	14 22.2%		0.8
Female	48 76.2%	49 77.8%		

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Table 2. Comparing clinical data finding between MS and control groups

Variable	Case group No(63) %	Control group No(63) %	χ^2	p-value
Smoking			0.5	
No	51 81.0%	54 85.7%		
Yes	12 19.0%	9 14.3%		0.4
D.M			0.0	
No	45 71.4%	45 71.4%		
Yes	18 28.6%	18 28.6%		1
HTN			0.9	
No	47 74.6%	42 85.7%		
Yes	16 25.4%	21 14.3%		0.4

Table 3. Genotype frequency of VDR (BsmI) between studied groups

BsmI	MS group No (63) %	Control group No (63) %	χ^2	p-value
BB	30 47.6	38 60.3%	7.2	**0.02***
Bb	22 34.9%	23 36.5%		
bb	11 17.5%	2 3.2%		

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Table 4. *Genotype frequency of VDR (TaqI) between studied groups*

TaqI	MS group No(63) %	Control group No(63) %	χ^2	p-value
TT	29 46.0%	23 36.5%	1.2	0.5
Tt	33 52.4%	39 61.9%		
Tt	1 1.6%	1 1.6%		

Table 5. Genotype frequency of IL7RA between studied groups

IL7RA	MS group No(63) %	Control group No(63) %	χ^2	p-value
CC	27 42.9%	43 68.2%	10.8	**0.004***
TT	8 12.7%	1 1.6%		
Ct	28 44.4%	19 30.2%		

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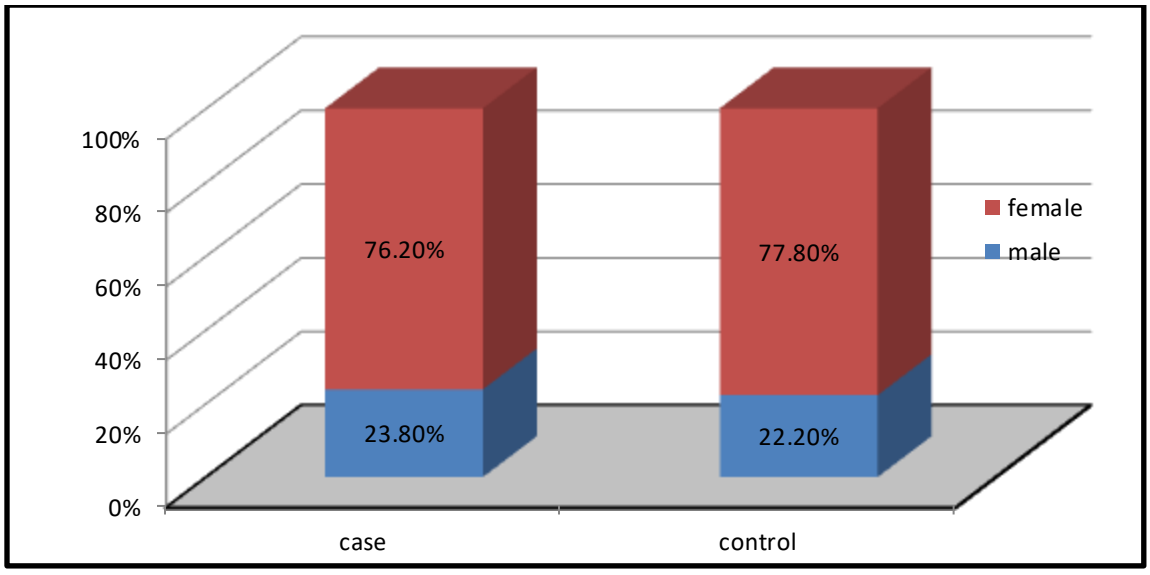

Fig 1. Demographic characteristics of the studied groups

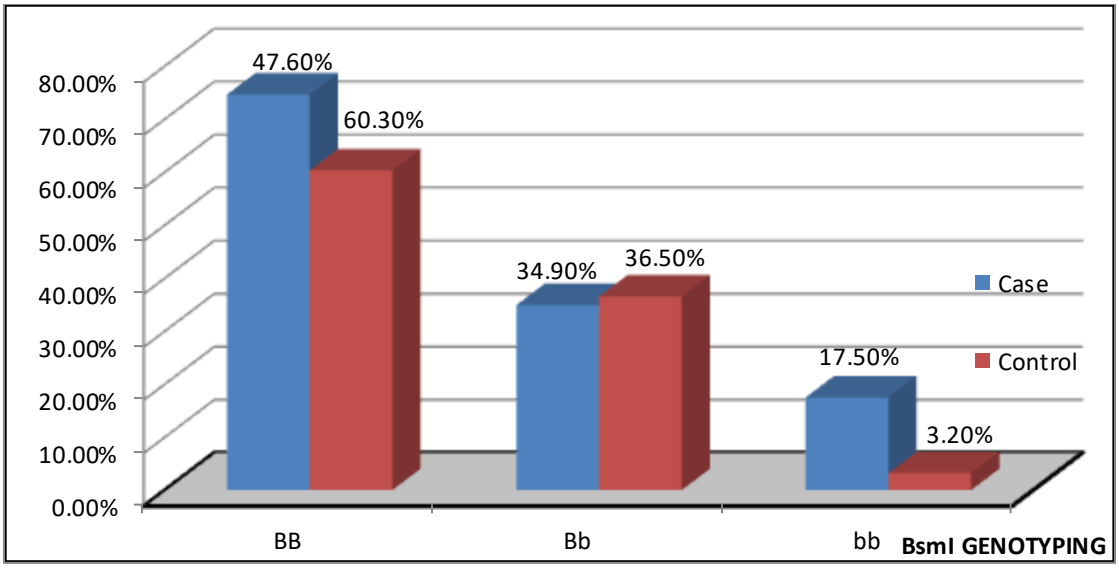

Fig 2. Distribution of frequency for VDR (BsmI) gene polymorphism in all studied groups.

DISCUSSION

Multiple sclerosis (MS) is a chronic neuroinflammatory disorder affecting the brain and spinal cord. More than two million individual around the world are distressed with MS mostly middle aged females. The disease represents a considerable cause of permanent disability in young adults[11].

The precise etiology of MS is still indistinct and it is thought to result from interplay between genetics and environment. The first and the most associated locus to MS is the major histocompatibility complex (MHC) that alone can interpret about 10% of MS genetics[12].

Genome wide association studies (GWAS) have listed many risk alleles that are linked with higher incidence of MS and could

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determine a genetic variant, located on chromosome X, was listed as MS risk allele. These loci can explain about 30% of MS pathogenesis[13].

Vitamin D which increases serum calcium level and regulates bone metabolism is now established to have immunomodulatory effects. It influences both cell mediated and humoral immune responses through distribution of its receptor among various immune cells. Vitamin D controls gene expression through its vitamin D responsive elements (VDRE) present on the DNA. It has been found that these VDRE are present in the active decondensed chromatin form in the immune cells compared to other body cells[14].

Concerning cell mediated immune response, active vitamin D acts mainly to suppress T cell proliferation. It inhibits both INF-ϒ producing Th1 cell and IL-17 producing Th17 cell which are associated with inflammation and autoimmunity. As a consequence immune response is shifted toward Th2 which antagonizes inflammation through production of IL-3, -4, -10. B cells proliferation is inhibited by vitamin D[15].

Regarding VDR gene polymorphisms (Bsm I), this study showed that Bsm I is associated with higher risk of MS (p=0.02). This finding was in agreement with[16-18]

On the other hand, [19-20] have showed discordant results to this study and reported no association between VDR SNP (Bsm I) and the risk of MS.

As for the VDR gene Taq I polymorphism, this study failed to find an association between the Taq I polymorphism and the risk developing of MS (p=0.5). This was in line with [21-22].Opposite to our finding, [23]reported a positive correlation between VDR (Taq I) SNP and MS risk.

This discrepancy of search results is due to variability in ethnicity and population genetic characteristics. MS has been reported to be polygenic disorder with multiple risk loci and interaction between these loci should be taken in consideration. Additionally differences in sample size, research tools, clinical type and disease severity of MS in patients involved in a certain study can explain such discripency.

In relation to IL7RA gene polymorphism (rs6897932), our study suggested a positive correlation between *IL7R* T244I polymorphism (rs6897932) polymorphism and MS (p=0.004).

This result is concordant with [24] who performed a meta-analysis to evaluate the *IL7R*T244I polymorphism association to MS. They confirmed that the *IL7R* T244I polymorphism is associated with MS. They reported that T244I influences differential splicing of exon 6 and that the C allele at rs6897932 is associated with more exon skipping, production of soluble IL7RA and associated with higher probability of MS. While the T allele is associated with less exon skipping and a membrane bound IL7RA production.

Moreover, [25] submitted eleven case-control studies in a meta-analysis, and reported that the IL7RA T244 I gene polymorphism is a predisposing factor for MS. He also confirmed that the C allele is more relevant to MS risk while T allele is associated with low risk.

However, [26] didn't find any significant positive relation of rs6897932 SNP and pathogenesis of MS. They attributed these findings to differences in populations' genetics and the interaction of many genetic loci in developing MS.

CONCLUSION

We conclude that VDR SNP (Bsm1) is one of the risk factors that participate in MS pathogenesis. Moreover IL7RA SNP is strongly related to MS development while VDR (Taq1) SNP is not a precipitating factor of MS in an Egyptian sample.

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