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An association study between FokI, BsmI, miR-146a, and miR-155 and Behcet's disease in the Egyptian population

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Abstract

Background: Behcet's disease (BD) is a systemic inflammatory disease of the blood vessels and affects various body parts. This study aimed to determine the association of four single-nucleotide polymorphisms (SNPs) and BD in the Egyptian population using multiple statistical models and show the resulting associations along with previous studies of different populations. Four SNPs were examined for their association with BD: two SNPs from vitamin D receptor gene (FokI and BsmI) were selected and the other two were selected from miR-146a and miR-155. These four SNPs were selected for their association and role with BD in different populations and in the immune system. A marker check was conducted using the Hardy-Weinberg equilibrium and minor allele frequency. The associations were tested using four different statistical models: multiplicative, dominant, recessive, and codominant models. All statistical models used the odd's ratio (OR) with confidence interval (CI) of 95% to evaluate the association of each SNP.

Results: BsmI showed association using the four models, while FokI did not show any association through any model. miR-155 showed association using the multiplicative and recessive models. miR-146a showed association using the multiplicative model only.

Conclusions: As a result, BsmI, miR-155, and miR-146a SNPs could have a role in the development of BD in the Egyptian population, while FokI could have a weak role, if any, in the development of BD in the Egyptian population.

Keywords: Behcet's disease, genetic association study, vitamin D receptor, microRNA, statistical models

Background

Behcet's disease (BD) is a rare disorder that causes vasculitis, that is, inflammation of the blood vessels, throughout the body. BD is unique among vasculitis-related diseases as it can affect small, medium, and large vessels [1, 2]. BD can have several signs and symptoms that may seem unrelated at first, such as mouth sores, eye inflammation, genital sores, and skin rashes and lesions. These symptoms vary from one person to another and may spontaneously resolve. Symptoms may also become less severe over time [3].

BD usually develops around the third or fourth decades. Generally, the sex distribution is roughly equal. However, male predominance is shown in some Middle Eastern and Mediterranean countries, while female predominance is shown in Japan and Korea. BD is particularly prevalent in regions along the "Silk Route," extending from Japan to the Middle East and Mediterranean countries, with Turkey having the highest prevalence where nearly 1/250 of the population aged ≥ 12 years have the disease. BD is rare in Western countries

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as only 0.64/100,000 of UK's population and only 0.33/100,000 of USA's population have the disease [4, 5].

Several immunological abnormalities have been previously reported; however, the exact cellular mechanism of the inflammatory changes remains unknown [3]. The most probable hypothesis is that the inflammatory reaction is set off by infectious agents or an autoantigen in genetically predisposed individuals.

To date, there is no specific treatment for BD. Medical practitioners currently attempt to suppress the inflammations caused by the disease to prevent any permanent damage. Patients are usually prescribed immunosuppressive and immunomodulatory agents and advised to improve their quality of life. Treatment typically involves medical practitioners from different disciplines, such as rheumatology and dermatology, and could also require help from a neurologist or cardiologist [6, 7].

This study aimed to investigate the direct association between BD and potential disease-causing single-nucleotide polymorphisms (SNPs). Four SNPs were examined for their association with BD: rs222850 (FokI) and rs1544410 (BsmI), which are both located on vitamin D receptor (*VDR*) gene; rs767649, which is located on the miRNA (microRNA) miR-155, and rs57095329, which is located on the miRNA miR-146a. These four SNPs were selected for their controversial association results with BD in different populations and their roles in the immune system [8–10].

VDR is found in the immune system cells. The importance of vitamin D comes from its effects on the immune system. An example is that it decreases interleukin (IL)-12 production and increases IL-10 production, resulting in the forestalling of the development of T-helper (Th)-1 and Th-17 cells [11]. Patients with autoimmune disorder commonly have vitamin D deficiency [11]. The two miRNAs (miR-155 and miR-146a) were studied by Zhou et al. [12] in 62 patients with ocular BD. They were categorized into three groups; control group with 20 individuals; BD group with active uveitis, which consisted of 23 individuals; and BD group without active uveitis, which consisted of 19 individuals. The study showed that miR-155 expression was significantly decreased in patients with active uveitis only, with no significant observations for the other two groups, suggesting that this result is exclusive to the BD group with active uveitis. These results are consistent with those of a previous study [13], which reported the excessive autoimmune response in the lungs of miR-155 knockout mice with marked leukocyte invasion.

Generally, miRNA control innate and adaptive immune responses and are therefore responsible for the development of inflammatory diseases [14]. miR-146a is part of multifunction miRNA "miR-146," which is responsible for restraining the production of pro-inflammatory tumor necrosis factor alpha (TNF-α), Th1 cell, and Th17 cell and enhancing apoptosis of dendritic cells (DCs) and stimulating regulatory T cells (Treg) [15]. Any genetic alterations in miR-146 could lead to massive production of IL-6 and TNF-α, which causes inflammatory disease [16]. In contrast, miR-155 is responsible for enhancing the production of inflammatory cytokines and stimulating Th2 immunity, Th1 and Th17 cell differentiation, antibody production, and B cell proliferation and activating DCs. Moreover, it also controls the expression of cytotoxic T-lymphocyte-associated protein in active T cells and is used as effector function in cluster of differentiation eight cells and natural killers [8, 17].

Methods

The four examined SNPs in our study are located in three chromosomes (5, 12, and 21), as shown in Table 1. Multiple statistical models were used for measuring the association of BD with the genotypes and alleles. Namely, the multiplicative, dominant, recessive, and co-dominant models were applied. They differ in the identification of the exposed and unexposed groups for both case and control categories. The odds ratio (OR) is used with its 95% confidence interval (CI) as a parameter to measure the case-control associations.

Patients

This study was conducted in the Egyptian population. There were 51 patients with BD and 45 controls for SNPs *VDR* (FokI, BsmI), and miR-155, while there were 51 patients with BD and 19 controls for miR-146a. Moreover, 82% of patients with BD were male, while

Table 1 Marker checks of the studied SNPs

	FokI	BsmI	*miR-155*	*miR-146a*
rsID	rs2228570	rs1544410	rs767649	rs57095329
Chromosome	12	12	21	5
Position (bp)	47879112	47846052	25572410	160467840
Alleles major:minor	F:f	B:b	A:T	A:G
Case count	51	51	51	51
Control count	45	45	45	19
MAF[a]	0.35	0.51	0.53	0.49
ObsHET[b] **(control)**	22	23	30	9
PredHET[c] **(control)**	21.6	20.3	22.2	8.6
HW *P*-value[d] **(control)**	0.901	0.376	0.0188	0.81
ObsHET[b] **(case)**	23	28	31	23
PredHET[c] **(case)**	21.6	23.8	24.5	25.3
HW *P*-value[d] **(case)**	0.638	0.213	0.059	0.509

[a]Minor allele frequency
[b]Observed heterozygosity
[c]Predicted heterozygosity
[d]Hardy-Weinberg *P*-value

80% of the controls were male for all SNPs, except that for the miR-146a, where all controls were male. The average age ± standard deviation (SD) of men with BD was 35 ± 8.7 years, while the average age ± SD of women with BD was 30.6 ± 6 years. The average age ± SD of male controls was 33.5 ± 9.7 years, while the average age ± SD of female controls was 33.8 ± 7.99 years. The average disease duration ± SD of men with BD was 5.3 ± 3.9 years, while that of women with BD was 5.6 ± 5.6 years.

Main outcome variable

The main outcome variable of this study was the chi-squared *P*-value where a significant association was indicated by a *P*-value < 0.05.

Other variables

A marker check was conducted for the conformance with the Hardy-Weinberg equilibrium (HWE) and minor allele frequency (MAF). The markers that were significantly deviated from HWE by a *P*-value < 0.01 were excluded from the rest of the study. The minimum accepted MAF was 0.01. A summary of the results of the marker check is shown in Table 1, along with information on each SNP.

Procedures

Anticoagulated peripheral blood specimens were obtained and stored at −20 °C until extraction was conducted. DNA was extracted from blood by QIAamplification DNA extraction kit (Qiagen, USA) according to the manufacturer's instructions. DNA quantification and purity assessment were conducted using the NanoDrop (ND)-1000 spectrophotometer (NanoDrop Technologies, Inc., Wilmington, USA). The FokI and BsmI polymorphisms were determined using these primers: Forward: 5'-AGCTGG CCC TGG CAC TGA CTA TGC TCT-3', Reverse: 5'-ATG GAA ACA CCT TGC TTC TCC CTC-3' for the FokI and Forward: 5'-CAA CCA AGA CTA CAA GTA CCG CGT CAG TGA-3', Reverse: 5'-AAC CAG CGC GAA GAG GTC AAG GG-3' for the BsmI (Metabion International AG, lena-christ-str. 44, 82152, Martinsried, Munich, Germany) [18].

The PCR amplification products were detected using gel electrophoresis and ultraviolet (UV) light transillumination. The PCR product size was 265 bp for FokI and 850 bp for BsmI. Regards FokI: DNA was denatured at 94 °C for 5 min, then the reaction mixture was subjected to denaturation for 30 s at 94 °C, annealing for 30 s at 61 °C, and extension for 1 min at 72 °C and this cycle was repeated to 35 cycles. The 265-bp PCR product of FokI was digested with 8 U FokI (BSeGI) restriction endonuclease overnight at 37 °C (Fermentas International Inc.). The digested products were separated on 4% agarose gel with ethidium bromide staining and UV transillumination, as shown in Fig. 1a. The FF genotype (homozygous of common allele) lacked a FokI restriction site and showed only one band of 265 bp. The ff genotype (homozygous of infrequent allele) generated two bands of 196 and 69 bp. The heterozygous displayed three fragments of 265, 196, and 69 bp, designated as Ff.

Regards BsmI: DNA was denatured at 94 °C for 5 min, then the reaction mixture was subjected to denaturation for 1 min at 94 °C, annealing for 1 min at 61 °C, and extension for 1.5 min at 72 °C and this cycle was repeated to 35 cycles. After amplification of the BsmI gene, the PCR product 850 bp was digested with restriction endonuclease BsmI enzyme after incubation at 37 °C (Fermentas International Inc.) overnight and electrophoresed in a 4% agarose gel containing ethidium bromide and then visualized by the UV transilluminator, as shown in Fig. 1b. Subjects

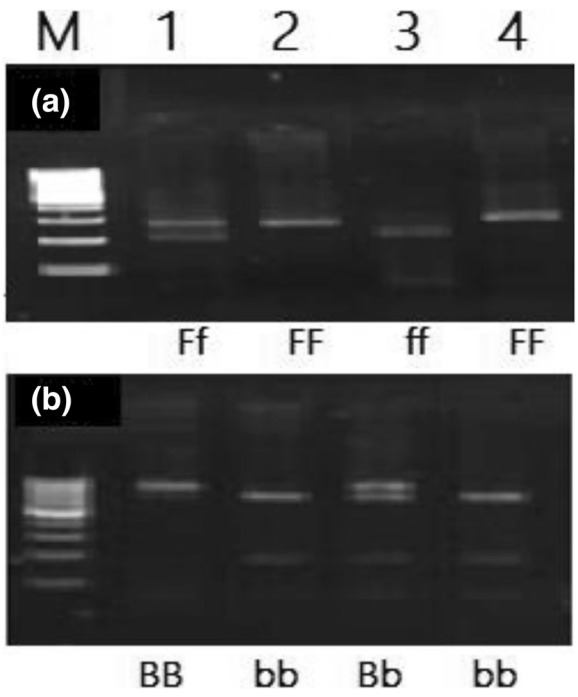

Fig. 1 Detection of the *VDR* SNPs through electrophoresis patterns of PCR amplification products. **a** 4% agarose gel stained with ethidium bromide and UV transillumination electrophoresis pattern for VDR FokI where: M: molecular weight marker (100 bp each); Lane 1: heterozygote (Ff) genotype with three bands at 265, 196, 69 bp; Lanes 2, 4: homozygote (FF) genotype with only one band at 265 bp; Lane 3: homozygote (ff) genotype with two bands at 196 and 69 bp. **b** 4% agarose gel stained with ethidium bromide and UV transillumination electrophoresis pattern for VDR BsmI where: M: molecular weight marker (100 bp each); Lane 1: homozygote (BB) genotype with only one band at 850 bp; Lanes 2, 4: homozygote (bb) genotype with two bands at 650 and 200 bp; Lane 3: heterozygote (Bb) genotype with three bands at 850, 650, and 200 bp

homozygote for the BsmI restriction site were designated bb and showed two fragments at 650 and 200 bp, while subjects homozygous for the absence of the site were designated BB. The homozygous type provided one band at 850 bp, and the heterozygous type provided three bands.

Genotyping for both miR-146a and miR-155 were performed using real-time PCR with TaqMan allelic discrimination assay (Applied Biosystems, USA). The primer/probe sets were synthesized with reporter dye FAM or VIC covalently linked at the 5′ end and quencher dye MGB linked to the 3′ end of the probe (Applied Biosystems, USA). The amplification of DNA was conducted in a total volume of 25 μL using a Rotor-Gene Q real-time PCR system (Qiagen, Valencia, CA, USA). The cycle condition was denaturation for 10 min at 95°C, followed by 45 cycles of 92°C for 15 s for annealing and then 60°C for 90 s for extension.

All participants were available for genotyping. All patients were recruited from the outpatient clinics of Cairo University Hospitals (Kasr El-Aini Hospital). The nature of the study was explained to all participants. All procedures followed were in accordance with the Helsinki Declaration of 1975, as revised in 2008. The study was approved by the Ethical Committee of the Faculty of Medicine, Cairo University, and oral and written consent was obtained from all participants. The Ethical Committee's reference number is I-151015. The ethics committee approved all consent procedures. All samples were withdrawn after obtaining written informed consent from the participants.

Statistical analysis

Analysis of variance was used to test whether the study is applicable or not based on the number of men in both BD and control groups along with their average age and SD. The resulting *P*-value was 0.474, which is greater than our threshold of 0.01. Therefore, we were able to move forward with the study. *P*-values of the statistical models were calculated using MedCalc (https://www.medcalc.org/calc/odds_ratio.php], while all graphs and other calculations (i.e., OR, CI, and population statistics) were calculated using Microsoft Excel. *P*-values < 0.05 were considered statistically significant. For each statistical model, the OR with 95% CI was calculated for each SNP to deduce the association.

Results

All four SNPs passed the MAF check and HWE conformance check. Table 2 shows the association between all four SNPs and BD. A graphical representation of the study is also shown in Fig. 2.

The *P*-value for each model was calculated, as shown in Table 2, and used to indicate the association of each SNP with different models.

Table 2 Case-2 control study and SNP analysis

		FokI	*BsmI*	miR-155	miR-146a
Multiplicative model	**P**	0.1644	**0.0001**[a]	**0.0341**[a]	**0.0403**[a]
	OR	1.526	3.205	0.5377	0.444
	95% CI	0.84086-2.7726	1.77377 - 5.79262	0.30285 - 0.95468	0.2047 - 0.96461
	Association	No	Yes Susceptive	Yes Protective	Yes Protective
Dominant model	**P**	0.2552	**0.0041**[a]	0.1025	0.1313
	OR	1.611	5.590	0.38043	0.423
	95% CI	0.708457-3.663641	1.72415 - 18.1296	0.11925 - 1.21364	0.13843-1.29301
	Association	No	Yes Susceptive	No	No
Recessive model	**P**	0.2446	**0.0012**[a]	**0.0332**[a]	0.0922
	OR	2.164	6.133	0.3	0.257
	95% CI	0.58943 - 7.9483	2.0439 - 18.4049	0.09909 - 0.90829	0.053 - 1.24953
	Association	No	Yes Susceptive	Yes Protective	No
Codominant Model with heterozygote	**P**	0.4113	**0.0351**[a]	0.2299	0.3765
	OR	1.43478	3.69643	0.48387	0.58696
	95% CI	0.60637 - 3.39498	1.09594 - 12.4674	0.14793 - 1.58274	0.18022 - 1.91164
	Association	No	Yes Susceptive	No	No
Codominant model with minor homozygote	**P**	0.171	**0.0002**[a]	**0.0173**[a]	0.0566
	OR	2.625	16.2	0.16667	0.1875
	95% CI	0.65921 - 10.4529	3.73156 - 70.3298	0.03811 - 0.72882	0.03355 - 1.04796
	Association	No	Yes Susceptive	Yes Protective	No

[a]Significant association

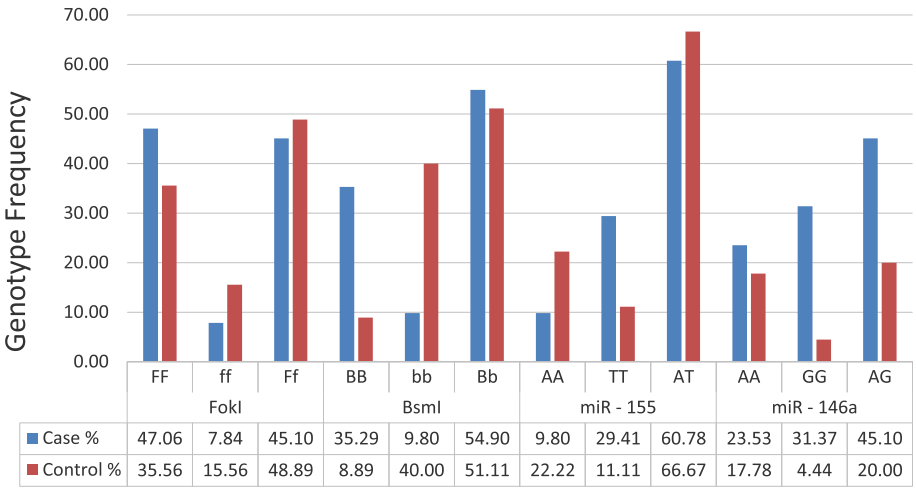

Fig. 2 Genotype distribution of patients with BD and controls for the four SNPs

Table 3 Association status with BD of this study and previous studies

	Population	No. of cases	No. of controls	Genotype	Genotype frequency (cases- controls)	Allele	Allele frequency (cases-controls)	Association with BD	References
FokI (rs2228570)	Egyptian (our study)	51	45					No	
	Turkish	37	30					No	[19]
	Iranian	50	50			f	0.26-0.13	Yes Protective	[20]
BsmI (rs1544410)	Egyptian (our study)	51	45	BB	0.352-0.088			Yes susceptive	
				bb	0.098-0.4			Yes protective	
				Bb	0.549-0.511			Yes susceptive	
						B	0.63-0.35	Yes susceptive	
						b	0.37-0.65	Yes protective	
	Iranian	50	50					No	[20]
	Tunisian	131	152					No	[21]
miR-155 (rs767649)	Egyptian (our study)	51	45	AA	0.098-0.222			Yes protective	
				TT	0.294-0.111			Yes susceptive	
						A	0.401-0.55	Yes protective	
						T	0.598-0.44	Yes susceptive	
miR-146a (rs57095329)	Egyptian (our study)	51	19			A	0.46-0.657	Yes protective	
	Chinese	809	1132					No	[22]
	Iranian	100	100					No	[23]

BsmI was significantly susceptible through all statistical models. FokI was not associated with BD. miR-155 showed association with the multiplicative, recessive, and codominant models using minor homozygote. miR-146a was only associated with the dominant model.

From Table 2, we can deduce the association between four SNPs (alleles and genotypes) associated with BD. FokI has shown no association with BD through all statistical models that were tested in this study. BsmI showed an association with BD through all genotypes and major allele (B). Furthermore, miR-155 showed that carriers of the genotype (TT) had a susceptive role in BD. Moreover, allele (A) is in a protective role against BD. In miR-146a, it was found that allele (A) holders have a protective association with BD. However, there was no association shown of the genotypes with BD.

Discussion

In this study, four SNPs were selected to be examined for possible association with BD. Two of these SNPs are from miRNA, and the other two are from the *VDR* gene. After examining FokI (rs222850), it was shown that it had no association with BD through all statistical models. In contrast, BsmI (rs15544410) had a susceptive association with BD. Both miR-155 (rs767649) and miR-146a (rs57095329) had a protective association with BD.

Previous studies have also inspected the association between some SNPs with BD. Other studies [19–23] inspected three of four SNPs selected for this study. However, these studies were performed on different populations; specifically, they were performed on Turkish, Iranian, Tunisian, and Chinese populations. A complete comparison of this study's results and five previous studies is shown in Table 3.

The results for FokI were in line with a Turkish study [19], possibly because both Turkey and Egypt are Mediterranean countries, where no association was found between the SNP and BD. However, an Iranian study [20] found a susceptive association between FokI and BD, which rebut the finding in the other two studies. This could be due to the different proportions of women; as in the Iranian study, it is almost half of their studied population, while in this study, it is only 20%.

There were several contradictions between the findings in this study and those of other studies regarding BsmI. An Iranian study [20] and Tunisian study [21] showed no association, while in this study, BsmI had significant susceptibility to BD. The contradiction could be due to the larger sample size (131 cases and 152 controls) in the Tunisian study and the larger number of women with BD (21 of 50 patients with BD) in the Iranian study.

Regarding miR-146a, previous studies, such as Chinese [22] and Iranian [23] studies, had matched the results in this study, since, in all studies, there was no association between SNP based on genotypes and BD. However, in this study, there was an association on the allele level. This could also be due to the larger sample size in the Chinese (809 cases and 1132 controls) and Iranian studies (100 cases and 100 controls) compared to our study (51 cases and 19 controls).

Conclusions

An association between *VDR* BsmI polymorphism, miR-146a, and miR-155 and BD was proven using different statistical models in our dataset. In our study, *VDR* BsmI had a susceptible association using all models, while *VDR* FokI polymorphism had no association with BD. miR-146a only showed protective association with the multiplicative model and miR-155 showed protective association through the multiplicative, recessive, and codominant minor homozygote models. In future work, an extension of data should be provided to achieve more tests with higher confidence and further investigate the association of different polymorphisms and miRNAs and BD in the Egyptian population.

Abbreviations

BD: Behcet's disease; CI: Confidence interval; DC: Dendritic cells; HWE: Hardy-Weinberg equilibrium; IL: Interleukin; MAF: Minor allele frequency; miRNA: MicroRNA; OR: Odd's ratio; SD: Standard deviation; SNPs: Single-nucleotide polymorphisms; Th: T-helper cell; TNF-α: Tumor necrosis factor alpha; Treg: Stimulating regulatory T cells; UV: Ultraviolet; VDR: Vitamin D receptor

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Not applicable.

Authors' contributions

All authors have read and approved the manuscript and agree with its submission to "Egyptian Journal of Medical Human Genetics." Conceptualization: MMM, MME, MNS, OGS. Data curation: MMM, MME, MNS, OGS. Formal analysis: MMM, MME. Investigation MMM, MME, MNS. Methodology: MMM, MME, MNS, OGS. Resources: OGS. Software: MMM, MME Supervision: MNS, MSM, MH, OGS. Validation: MMM, MME, MNS. Visualization: MMM, MME, MNS. Writing—original draft: MMM, MME. Writing—review & editing: MNS, MSM, MH, OGS

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Availability of data and materials

All data in the present study are available from the corresponding authors upon a reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethical Committee of the Faculty of Medicine, Cairo University, and oral and written consent was obtained from all participants. The Ethical Committee's reference number is I-151015 The Ethical Committee approved all consent procedures. All samples were collected after obtaining written informed consent from the participants.

Consent for publication

The study obtained consent for publication.

Competing interests
There are no competing interests associated with the manuscript.

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