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ORIGINAL ARTICLE

Protein tyrosine phosphatase non-receptor type 2 (PTPN2) gene polymorphisms (rs2542151, rs7234029) in Egyptian Behçet's disease patients: a preliminary report

Doaa H. S. Attia[1] · Marwa Alkaffas[2] · Mervat Eissa[1] · Laila Rashed[2] · Rasha A. M. Khattab[3] · Radwa Elzanaty[4] · Rabab A. Khattab[5] · Lamees A. Samy[6]

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Abstract

Single nucleotide polymorphisms (SNPs) of the protein tyrosine phosphatase non-receptor type 2 (*PTPN2*) gene have been documented to be linked with several autoimmune disorders including Behçet's disease (BD). *PTPN2* SNPs rs2542151 and rs7234029 have been assessed using real-time PCR in 96 BD patients and 50 controls matched by age and gender. Patients were categorized into groups according to the disease phenotypes and severity. A total of 94.8% of patients were males. The patients' mean age at onset was 26.1 ± 8 years. The median (IQR) disease duration was 8.5(4–13) years. No difference was observed between the patients and controls concerning the frequency of the two SNPs' different genotypes, models, and alleles. Moreover, neither disease phenotypes nor severity were associated with rs2542151 or rs7234029 SNPs. *PTPN2* rs2542151 and rs7234029 SNPs do not seem to have associations with BD occurrence, phenotypes, or severity in the Egyptian patients.

Key Points

- *PTPN2 rs2542151 and rs7234029 SNPs do not seem to have associations with BD occurrence, phenotypes, or severity in the Egyptian patients.*
- *Further studies involving a larger sample size with variable clinical diversity are recommended to verify the results.*

Keywords Behçet's disease · Polymorphisms · Protein tyrosine phosphatase non-receptor type 2 · *PTPN2* · SNPs

What is already known about this subject?

A genetic contribution was suggested to influence BD development and phenotypic expression. HLA-B51 contributes to less than 20% of the genetic predisposition to BD development. Many non-HLA genes were studied including the protein tyrosine phosphatase non-receptor type 2 (PTPN2). PTPN2 SNPs have been documented to be linked with several autoimmune disorders. Very scarce data exist regarding the relation between PTPN2 and BD.

What does this study add?

This work aimed to study the relation between PTPN2 SNPs (rs2542151 T → G and rs7234029 A → G) and BD development, phenotypic expression, and severity. The study showed no difference between the patients and controls concerning the frequency of the two SNPs' different genotypes, models, and alleles. Moreover, neither disease phenotypes nor severity were associated with rs2542151 or rs7234029 SNPs.

How might this impact on clinical practice?

PTPN2 rs2542151 and rs7234029 SNPs do not seem to contribute to the pathogenesis of BD in the Egyptian patients. Further work is needed to identify the genetic risk factors contributing to the disease development, phenotypic expression, and severity in the different ethnicities helping the development of future effective therapeutic agents.

Extended author information available on the last page of the article

Introduction

Behçet's disease (BD) is an inflammatory disease characterized by a relapsing course. It can potentially impact all organ systems; however, it is most likely to affect the vascular, neurological, mucocutaneous, and articular systems. Gender differences have been described globally. Males exhibit a higher prevalence of the disease in the Mediterranean region, whereas females are disproportionately afflicted in the Far East [1]. It is hypothesized that it incorporates characteristics of autoimmunity and autoinflammation. The exact mechanism by which BD develops is unknown. Although the disease risk factors remain unknown, genetic and environmental influences appear to be significant [2].

Patients with BD express different disease phenotypes in isolation or combination. Factors favoring the expression of a particular phenotype are not fully understood; however, a genetic contribution was suggested [3]. Identifying the environmental and genetic risk factors could help in understanding the disease pathogenesis and the phenotype-genotype interactions with the subsequent development of effective therapeutic agents.

Human leukocyte antigen (HLA)-B51 was the first studied gene in BD. It was thought to have the most potent genetic predisposition to the disease. However, it contributes to less than 20% of the genetic predisposition to the disease [4]. Many non-HLA genes were studied. Among the studied non-HLA genes is the protein tyrosine phosphatase non-receptor type 2 (*PTPN2*) gene [5, 6].

In cell cycle regulation and signal transduction, protein tyrosine phosphatases (PTPs) are crucial regulatory enzymes. Non-receptor-type PTPs (PTPN22, SHP-1, PTPN2, and PTP-PEST) are distinguished from receptor-type PTPs (CD45 and CD148) [6, 7].

Chromosome 18p11 contains the *PTPN2* gene. The term T cell protein tyrosine phosphatase (TC-PTP) is applied to its protein product [8]. It is a key regulatory factor of T-cell-mediated immune response through suppression of the Janus kinase/signal transducers and activators of transcription (JAK/STAT) signaling pathway following T cell and cytokines receptors activation [9–12]. PTPN2-deficient mice were found to express systemic inflammation and die shortly after birth [7, 13]. Moreover, it has been documented that *PTPN2* single nucleotide polymorphisms (SNPs) are linked to dysfunctional protein products with subsequent increment of proinflammatory cytokines production [14], upregulation of Th2 and Th17, downregulation of T_{Reg}, and the development of autoimmunity [15].

Numerous studies addressed the role of *PTPN2* SNPs in several autoinflammatory/autoimmune diseases like inflammatory bowel disease (IBD) [14, 16–18], juvenile idiopathic arthritis [19], rheumatoid arthritis [20, 21], and type I diabetes mellitus [22–26].

Notably, Crohn's disease (CD) and BD share common characteristics: (1) common age at onset, (2) common relapsing course, (3) major role of the innate immune system in the pathogenesis of both diseases, (4) contribution of normal flora of oral mucosa in BD pathogenesis and intestinal microbiota in CD pathogenesis, (5) gastrointestinal involvement that could be indistinguishable between the two diseases, (6) extraintestinal features that are common between both diseases, i.e., mucocutaneous, musculoskeletal, ocular, and vascular, (7) some patients with intestinal BD may be mismanaged as cases of CD while some CD patients could satisfy the classification criteria of BD [27–29].

While *PTPN2* SNPs are extensively studied in CD [14, 16–18], few studies addressed the association between *PTPN2* polymorphisms and BD in Chinese patients [5, 6]; and no data are available about other ethnicities. As most of the autoimmune rheumatic diseases show polygenic inheritance with shared susceptibility loci between different diseases [30, 31] and based on the aforementioned perspectives, this work aimed to study *PTPN2* SNPs (rs2542151 T → G and rs7234029 A → G) in Egyptian BD patients trying to find a relation between the two SNPs and disease occurrence, phenotypes and severity.

Materials and methods

Study design and data acquisition

Ninety-six adult patients were recruited from the Rheumatology and Rehabilitation Department and Outpatient Clinic of Kasr Al-Ainy Hospital, Cairo University. Fifty apparently healthy age- and sex-matches persons were included as control subjects. The 2006 International Study Group Criteria for BD were used for patients' classification [32]. Patients with overlap syndromes were excluded.

All patients underwent thorough history taking, clinical examination, and laboratory testing. Ophthalmological assessment of patients was carried out in the Ophthalmology Department of Kasr Al-Ainy Hospital, Cairo University. The epidemiological features in addition to the clinical characteristics were collected from medical files using a standardized form (Table S1). Disease onset was defined as the time point of occurrence of the initial disease manifestation. Disease duration referred to the duration between the disease onset and enrollment in the study.

Patients were categorized into six phenotypes according to the involved organ system(s): mucocutaneous, ocular, neurological, peripheral vascular, musculoskeletal, and gastrointestinal phenotypes.

The disease severity score was calculated as suggested by Yosipovitch et al. (1995) [33] and modified by Krause et al. (2001) [34] categorizing the patients into one of three groups: mild, moderate, and severe. The presence of one of the severe manifestations is sufficient to categorize the patient as having a severe disease. The same applies to the moderately severe manifestations; otherwise, the patient is categorized as having a mild disease. Each mild, moderate, and severe item is given 1, 2, and 3 points, respectively, with the final score calculated as the sum of the total items reflecting the cumulative number of manifestations the patient has.

This research investigation received approval from the Research Ethics Committee of Faculty of Medicine, Cairo University (N-51–2023), and it conformed to the 1964 Helsinki Declaration and its subsequent revisions. Each subject provided an informed consent.

SNP genotyping assay

Genotyping was performed using real-time polymerase chain reaction (PCR) with TaqMan allelic discrimination assay (Applied Biosystems, USA).

Table 1 Demographic features, clinical manifestations, and disease severity of the patient group

Characteristics ($N=96$)		
Gender	Males, *N* (%)	91(94.8)
	Females, *N* (%)	5(5.2)
Constitutional manifestations, *N* (%)		22(22.9)
Mucocutaneous manifestations, *N* (%)		96(100)
Oral ulcers, *N* (%)		94(97.9)
Genital ulcers, *N* (%)		76(79.2)
Musculoskeletal involvement, *N* (%)		21(21.9)
Pulmonary vascular involvement, *N* (%)		7(7.3)
Ocular involvement, *N* (%)		63(65.6)
Neurological involvement, *N* (%)		28(29.2)
GIT involvement, *N* (%)		4(4.2)
Peripheral vascular disease, *N* (%)		28(29.2)
Deep venous thrombosis, *N* (%)		27(28.1)
Peripheral arterial disease, *N* (%)		7(7.3)
Great vein disease, *N* (%)		7(7.3)
Aortic aneurysm, *N* (%)		2(2.1)
Cardiac involvement, *N* (%)		1(1)
Disease severity	Mild, *N* (%)	5(5.2)
	Moderate, *N* (%)	11(11.5)
`	Severe, *N* (%)	80(83.3)
Age at onset, years, mean ± SD		26.1 ± 8
Disease duration, years, median (IQR)		8.5(4–13)
Disease severity score, median (IQR)		6(5–8)

N number, *GIT* gastrointestinal, *IQR* interquartile range

Peripheral blood samples in EDTA vacutainers were withdrawn from each patient to be stored below 20 °C until DNA extraction was performed. A 50 bp ladder (GeneRuler TM) was used to determine the size of the PCR fragments. Detection of *PTPN2* gene polymorphisms (rs2542151 and rs7234029) was conducted using allelic discrimination assay by Applied Biosystems (ABI) 7500 real-time PCR system (Foster City, CA, USA).

Thermal cycling was designed for 10 min for the initial denaturation cycle at 95 °C, then 50 cycles were conducted for 15 s at 95 °C, and finally, a 1-min cycle at 60 °C. The Lot. No. for the utilized Taq Man genotyping master mix from Applied Biosystems was 01245069. Genotyping was done in the PCR Unit of the Clinical and Chemical Pathology Department, Kasr Al-Ainy Hospital, Cairo University.

Statistical methods

Data were coded and entered using the statistical package for the Social Sciences (SPSS) version 28 (IBM Corp., Armonk, NY, USA). Data were summarized using means and standard deviations for the normally distributed quantitative variables, medians and interquartile ranges for the non-normally distributed quantitative variables; and frequencies (number of cases) and relative frequencies (percentages) for categorical variables. Comparisons between numerical variables were done using the non-parametric Kruskal–Wallis test and Mann–Whitney test as appropriate [35]. For comparing categorical data, chi-square ($\chi 2$) test was performed. The exact test was used instead when the expected frequency was less than 5 [36]. Odds ratio (OR) with 95% confidence intervals were calculated. *P*-values less than 0.05 were considered statistically significant.

Power analysis of the current study was done on comparing genotypes between cases and controls, and between disease severity categories using our results as effect size. The chi-squared and Fisher exact tests for independent samples were chosen to perform the power analysis; the α-error level was fixed at 0.05. When the frequency table includes the value, "zero", we added the category to the nearest one to perform the analysis. The percentage of each genotype was entered with the corresponding sample size in each group. Calculations were done using G*Power software version 3.1.9.6 for MS Windows, Franz Faul, Kiel University, Germany.

Results

This study included 96 BD patients, 94.8% of whom were males. The patients' mean age at onset was 26.1 ± 8 years. The median (IQR) disease duration was 8.5 (4–13) years.

The proportions of patients in the six phenotypes were 100%, 65.6%, 29.2%, 29.2%, 21.9%, and 4.2% for the mucocutaneous, ocular, peripheral vascular, neurological, musculoskeletal, and gastrointestinal phenotypes, respectively.

Clinical manifestations and disease severity of the patients are presented in Table 1. The median (IQR) severity score was 6 (5–8).

No significant difference was observed between the patients and controls regarding the frequency of the two SNPs' different genotypes, genetic models, and alleles, as shown in Table 2.

Table 3 shows the association between *PTPN2* rs2542151 and the sex, age at disease onset, clinical characteristics, and disease severity at the genotypes, genetic models, and alleles levels. The comparisons revealed an association between the SNP and neurological involvement under the recessive model ($p = 0.044$, OR (95% CI)= 4.7 (1.0–21.3)).

There was no association between *PTPN2* rs7234029 and the sex, age at disease onset, clinical characteristics, and disease severity at the genotypes, genetic models, and alleles levels, as shown in Table 4.

Regarding the relation between *PTPN2* SNPs rs2542151 and rs7234029 and the different disease phenotypes, only four phenotypes were included in the statistical analysis: the musculoskeletal, ocular, peripheral vascular, and neurological phenotypes. The mucocutaneous phenotype was excluded as it was universal in all patients. Patients showing an overlap of two or more phenotypes, excluding the mucocutaneous one, were excluded as well. Finally, 46 patients were included in the analysis: 3 patients with the musculoskeletal phenotype, 28 patients with the ocular phenotype, 6 patients with the neurological phenotype, and 9 patients with the peripheral vascular phenotype. Each one has the mucocutaneous phenotype plus one of the other four phenotypes. The analysis revealed that neither rs2542151 nor rs7234029 was associated with the disease phenotypes (Table 5).

The study has a power of 81.6% and 90.3% for testing the association between the *PTPN2* SNPs rs2542151, and disease occurrence and severity category, respectively. On the other side, the corresponding power for the other SNP, rs7234029, was 20.6% and 44.4%, respectively.

Discussion

Based on the previously reported association between *PTPN2* SNPs and different autoimmune diseases [14–26] and the scarcity of data about BD [5, 6], we investigated *PTPN2* SNPs (rs2542151 T → G and rs7234029 A → G) in Egyptian patients with BD trying to find an association with disease susceptibility, phenotypic expression, and severity.

Regarding the prevalence of the two SNPs' various genotypes, models, and alleles, we found no distinction between

Table 2 Comparisons between patients and controls regarding genotypes, models, and alleles frequencies of PTPN2 SNPs rs2542151 and rs7234029

SNP				Cases *N* (%) *N* = 96	Controls *N* (%) *N* = 50	*p* value	OR(95%CI)
PTPN2 rs2542151	Genotypes		GG	8(8.3)	2(4)	0.288	
			GT	31(32.3)	12(24)		
			TT	57(59.4)	36(72)		
	Models	Dominant	GG + GT	39(40.6)	14(28)	0.132	1.8(0.8–3.7)
			TT	57(59.4)	36(72)		
		Recessive	GG	8(8.3)	2(4)	0.495	2.2(0.4–10.7)
			GT + TT	88(91.7)	48(96)		
	Alleles		G	47(24.5)	16(16)	0.095	1.7(0.9–3.2)
			T	145(75.5)	84(84)		
PTPN2 rs7234029	Genotypes		GG	6(6.2)	3(6)	0.994	
			AG	28(29.2)	15(30)		
			AA	62(64.6)	32(64)		
	Models	Dominant	GG + AG	34(35.4)	18(36)	0.944	1(0.5–2)
			AA	62(64.6)	32(64)		
		Recessive	GG	6(6.2)	3(6)	> 0.999	1(0.3–4.4)
			AG + AA	90(93.8)	47(94)		
	Alleles		G	40(20.8)	21(21)	0.973	1(0.5–1.8)
			A	152(79.2)	79(79)		

PTPN2 protein tyrosine phosphatase non-receptor type 2, *SNP* single nucleotide polymorphism, *N* number, *OR* odds ratio, *CI* confidence interval. Comparisons were done using the chi-square tests

Table 3 The associations between PTPN2 SNP rs2542151 genotypes, models, and alleles; and the demographic and clinical characteristics as well as disease severity of the patients group

Characteristics		Genotypes $N=96$				Models								Alleles $N=192$			
						Dominant $N=96$				Recessive $N=96$							
		GG ($N=8$)	GT ($N=31$)	TT ($N=57$)	*p* value	GG+GT ($N=39$)	TT ($N=57$)	*p* value	OR(95%CI)	GG ($N=8$)	GT+TT ($N=88$)	*p* value	OR(95%CI)	G ($N=47$)	T ($N=145$)	*p* value	OR(95%CI)
Gender	Females, *N* (%)	0(0)	0(0)	5(8.8)	0.165	0(0)	5(8.8)	0.078		0(0)	5(5.7)	>0.999	—	0(0)	10(6.9)	0.123	—
	Males, *N* (%)	8(100)	31(100)	52 (91.2)		39(100)	52(91.2)			8(100)	83(94.3)			47(100)	135(93.1)		
Constitutional manifestations, *N* (%)		2(25)	8(25.8)	12(21.1)	0.870	10(25.6)	12(21.1)	0.599	1.3(0.5–3.4)	2(25)	20(22.7)	>0.999	1.1(0.2–6.1)	12(25.5)	32(22.1)	0.624	1.2(0.6–2.6)
Oral ulcers, *N* (%)		8(100)	29(93.5)	57(100)	0.117	37(94.9)	57(100)	0.162	—	8(100)	86(97.7)	>0.999	—	45(95.7)	143(98.6)	0.252	0.3(0–2.3)
Genital ulcers, *N* (%)		7(87.5)	24(77.4)	45(78.9)	0.820	31(79.5)	45(78.9)	0.949	1(0.4–2.8)	7(87.5)	69(78.4)	>0.999	1.9(0.2–16.6)	38(80.9)	114(78.6)	0.744	1.1(0.5–2.6)
Musculoskeletal involvement, *N* (%)		0(0)	7(22.6)	14(24.6)	0.288	7(17.9)	14(24.6)	0.441	0.7(0.2–1.9)	0(0)	21(23.9)	0.194		7(14.9)	35(24.1)	0.183	0.6(0.2–1.3)
Pulmonary vascular involvement, *N* (%)		1(12.5)	2(6.5)	4(7)	0.835	3(7.7)	4(7)	>0.999	1.1(0.2–5.2)	1(12.5)	6(6.8)	0.467	2(0.2–18.6)	4(8.5)	10(6.9)	0.749	1.3(0.4–4.2)
Ocular involvement, *N* (%)		7(87.5)	18(58.1)	38(66.7)	0.285	25(64.1)	38(66.7)	0.795	0.9(0.4–2.1)	7(87.5)	56(63.6)	0.256	4(0.5–34)	32(68.1)	94(64.8)	0.683	1.2(0.6–2.3)
Neurological involvement, *N* (%)		5(62.5)	7(22.6)	16(28.1)	0.083	12(30.8)	16(28.1)	0.775	1.1(0.5–2.8)	5(62.5)	23(26.1)	***0.044***	4.7(1–21.3)	17(36.2)	39(26.9)	0.224	1.5(0.8–3.1)
GIT involvement, *N* (%)		0(0)	2(6.5)	2(3.5)	>0.665	2(5.1)	2(3.5)	>0.999	1.5(0.2–11)	0(0)	4(4.5)	>0.999	—	2(4.3)	6(4.1)	>0.999	1(0.2–5.3)
Peripheral vascular disease, *N* (%)		2(25)	11(35.5)	15(26.3)	0.641	13(33.3)	15(26.3)	0.458	1.2(0.7–2)	2(25)	26(29.5)	>0.999	0.8(0.2–4.2)	15(31.9)	41(28.3)	0.633	1.2(0.6–2.4)
Deep venous thrombosis, *N* (%)		2(25)	11(35.5)	14(24.6)	0.541	13(33.3)	14(24.6)	0.348	1.5(0.6–3.8)	2(25)	25(28.4)	>0.999	0.8(0.2–4.4)	15(31.9)	39(26.9)	0.506	1.3(0.6–2.6)
Peripheral arterial disease, *N* (%)		0(0)	3(9.7)	4(7)	0.639	3(7.7)	4(7)	>0.999	1.1(0.2–5.2)	0(0)	7(8)	>0.999	—	3(6.4)	11(7.6)	>0.999	0.8(0.2–3.1)
Great vein disease, *N* (%)		0(0)	2(6.5)	5(8.8)	0.655	2(5.1)	5(8.8)	0.697	0.6(0.1–3.1)	0(0)	7(8)	>0.999	—	2(4.3)	12(8.3)	0.524	0.5(0.1–2.3)
Aortic aneurysm, *N* (%)		0(0)	1(3.2)	1(1.8)	0.819	1(2.6)	1(1.8)	>0.999	1.5(0.1–24.3)	0(0)	2(2.3)	>0.999	—	1(2.1)	3(2.1)	>0.999	1(0.1–10.1)
Cardiac involvement, *N* (%)		0(0)	0(0)	1(1.8)	0.708	0(0)	1(1.8)	>0.999		0(0)	1(1.1)	>0.999	—	0(0)	2(1.4)	>0.999	—
Disease severity	Mild, *N* (%)	0(0)	3(9.7)	2(3.5)	0.393	3(7.7)	2(3.5)	0.606	—	0(0)	5(5.7)	0.418	—	3(6.4)	7(4.8)	0.904	—
	Moderate, *N* (%)	0(0)	5(16.1)	6(10.5)		5(12.8)	6(10.5)			0(0)	11(12.5)			5(10.6)	17(11.7)		
	Severe, *N* (%)	8(100)	23(74.2)	49(86)		31(79.5)	49(86)			8(100)	72(81.8)			39(83)	121(83.4)		
Age at onset, years, median (IQR)		22(20–26.5)	24(21–32)	26(21–30)	0.516	24(21–30)	26(21–30)	0.490	—	22(20–26.5)	25(21–30)	0.268	—	24(21–28)	25(21–30)	0.287	—
Disease duration, years, median (IQR)		7(4–10.5)	8(5.5–12.5)	9(4–13)	0.625	8(5–12)	9(4–13)	0.934	—	7(4–10.5)	9(4–13)	0.353	—	8(5–12)	9(4–13)	0.624	—

Table 3 (continued)

Characteristics	Genotypes $N=96$				Models							Alleles $N=192$			
					Dominant $N=96$				Recessive $N=96$						
	GG ($N=8$)	GT ($N=31$)	TT ($N=57$)	*p* value	GG+GT ($N=39$)	TT ($N=57$)	*p* value	OR(95%CI)	GG ($N=8$)	GT+TT ($N=88$)	*p* value	OR(95%CI)	G ($N=47$)	T ($N=145$)	*p* value	OR(95%CI)
Disease severity score, median (IQR)	8(5–9.5)	6(5–7.5)	6(5–8)	0.509	6(5–8)	6(5–8)	0.862	—	8(5–9.5)	6(5–8)	.257	—	6(5–8)	6(5–8)	0.511	—

PTPN2 protein tyrosine phosphatase non-receptor type 2, *SNP* single nucleotide polymorphism, *N* number, *OR* odds ratio, *CI* confidence interval, *GIT* gastrointestinal. Comparisons were done using the chi-square tests for the qualitative variables and the Kruskal–Wallis or Mann–Whitney tests for the quantitative variables, as appropriate

BD patients and controls. Analyzing the association between the two SNPs and the different disease phenotypes and severity revealed an association between rs2542151 SNP and neurological involvement under the recessive model; however, with a marginal *p*-value and a wide 95% CI (p = 0.044, OR (95% CI)= 4.7 (1.0–21.3)).

Our results agree with Wu and colleagues who reported a weak association between *PTPN2* rs2542151 GT genotype and BD risk ($p=0.024$) in their Chinese Han population. This association was noted with the initial statistical analysis; however, it did not withstand after Bonferroni correction. On the contrary, the same SNP was associated with gastrointestinal involvement when patients were compared with the controls ($p=0.032$). Conversely, rs7234029 SNP did not show any association [5].

In disagreement with the study mentioned above and ours, Zhang et al. reported an increased risk of ocular BD development with the *PTPN2* SNP rs7234029 AG genotype ($p=3.33\times10^{-8}$, OR = 1.549) while the risk was lower with the AA ($p=1.10\times10^{-3}$, OR = 0.772) and GG ($p=1.94\times10^{-5}$, OR = 0.466) genotypes in their Han Chinese cohort with ocular BD. Moreover, these associations were observed with the co-dominant, dominant, recessive, and overdominant models. The previous associations were reported in men but not in women. Regarding the extra-ocular disease manifestations, the aforementioned SNP exhibited a significant correlation with genital ulcers, cutaneous lesions, and a positive pathergy test. Nevertheless, the authors acknowledged that this result might be biased by the predominance of males in their cohort [6].

On the contrary, *PTPN2* rs2542151 SNP did not show any association. Interestingly, the authors found significantly decreased *PTPN2* mRNA expression with the AA and AG genotypes compared with the GG genotype ($p=0.014$ and 0.019, respectively). Moreover, TNF-α production was significantly lower with the GG genotype compared with the AA or AG genotypes [6].

The different ethnicities, population characteristics, and sample size as well as the influence of environmental and other genetic factors could explain the discrepancy between our study and others.

Being the first study of PTPN2 in Egyptian BD patients, this preliminary study was commenced using a representative sample of patients and controls: 96 patients and 50 control subjects. After getting the results, power analyses of the study were performed. The study has a power of 81.6% and 90.3% for testing the association between the *PTPN2* SNP rs2542151, and disease occurrence and severity category, respectively. On the other side, the corresponding power for the other SNP, rs7234029, was 20.6% and 44.4%, respectively, probably due to the weak association between this SNP and the disease. Moreover, the population of this study showed limited heterogeneity: 94.8% of the study cohort were males; 80% of patients

Table 4 The association between PTPN2 SNP rs7234029 genotypes, models, and alleles; and the demographic and clinical characteristics as well as disease severity

Characteristics		Genotypes *N* = 96				Models								Alleles *N* = 192			
						Dominant *N* = 96				Recessive *N* = 96							
		GG (*N* = 6)	AG (*N* = 28)	AA (*N* = 62)	*p* value	GG + AG (*N* = 34)	AA (*N* = 62)	*p* value	OR(95%CI)	GG (*N* = 6)	AG + AA (*N* = 90)	*p* value	OR(95%CI)	G (*N* = 40)	A (*N* = 152)	*p* value	OR(95%CI)
Gender	Females, *N* (%)	1(16.7)	2(7.1)	2(3.2)	0.316	3(8.8)	2(3.2)	0.343	2.9(0.5–18.3)	1(16.7)	4(4.4)	0.281	4.3(0.4–46)	4(10)	6(3.9)	0.221	2.7(0.7–10.1)
	Males, *N* (%)	5(83.3)	26(92.9)	60(96.8)		31(91.2)	60(96.8)			5(83.3)	86(95.6)			36(90)	146(96.1)		
Constitutional manifestations, *N* (%)		2(33.3)	5(17.9)	15(24.2)	0.660	7(20.6)	15(24.2)	0.688	0.8(0.3–2.2)	2(33.3)	20(22.2)	0.618	1.8(0.3–10.3)	9(22.5)	35(23)	0.944	1(0.4–2.2)
Oral ulcers, *N* (%)		6(100)	28(100)	60(96.8)	0.571	34(100)	60(96.8)	0.538	––	6(100)	88(97.8)	> 0.999	––	40(100)	148(97.4)	0.582	—
Genital ulcers, *N* (%)		4(66.7)	20(71.4)	52(83.9)	0.299	24(70.6)	52(83.9)	0.125	0.5(0.2–1.3)	4(66.7)	72(80)	0.601	0.5(0.1–2.9)	28(70)	124(81.6)	0.109	0.5(0.2–1.2)
Musculoskeletal involvement, *N* (%)		2(33.3)	9(32.1)	10(16.1)	0.184	11(32.4)	10(16.1)	0.066	2.5(0.9–6.7)	2(33.3)	19(21.1)	0.609	1.9(0.3–11)	13(32.5)	29(19.1)	0.608	2(0.9–4.4)
Pulmonary vascular involvement, *N* (%)		0(0)	3(10.7)	4(6.5)	0.600	3(8.8)	4(6.5)	0.695	1.4(0.3–6.7)	0(0)	7(7.8)	> 0.999	––	3(7.5)	11(7.2)	> 0.999	1(0.3–3.9)
Ocular involvement, *N* (%)		3(50)	22(78.6)	38(61.3)	0.197	25(73.5)	38(61.3)	0.227	1.8(0.7–4.4)	3(50)	60(66.7)	0.411	0.5(0.1–2.6)	28(70)	98(64.5)	0.513	1.3(0.6–2.7)
Neurological involvement, *N* (%)		3(50)	7(25)	18(29)	0.473	10(29.4)	18(29)	0.969	1(0.4–2.6)	3(50)	25(27.8)	0.353	2.6(0.5–13.7)	13(32.5)	43(28.3)	0.602	1.2(0.6–2.6)
GIT involvement, *N* (%)		0(0)	0(0)	4(6.5)	0.318	0(0)	4(6.5)	0.294	––	0(0)	4(4.4)	> 0.999	––	0(0)	8(5.3)	0.208	—
Peripheral vascular disease, *N* (%)		2(33.3)	7(25)	19(30.6)	0.839	9(26.5)	19(30.6)	0.667	0.8(0.3–2.1)	2(33.3)	26(28.9)	> 0.999	1.2(0.2–7.1)	11(27.5)	45(29.6)	0.794	0.9(0.4–2)
Deep venous thrombosis, *N* (%)		2(33.3)	7(25)	18(29)	0.886	9(26.5)	18(29)	0.789	0.9(0.3–2.3)	2(33.3)	25(27.8)	> 0.999	1.3(0.2–7.5)	11(27.5)	43(28.3)	0.921	1(0.4–2.1)
Peripheral arterial disease, *N* (%)		0(0)	1(3.6)	6(9.7)	0.457	1(2.9)	6(9.7)	0.415	0.3(0–2.5)	0(0)	7(7.8)	> 0.999	––	1(2.5)	13(8.6)	0.308	0.3(0–2.2)
Great vein disease, *N* (%)		1(16.7)	3(10.7)	3(4.8)	0.403	4(11.8)	3(4.8)	0.240	2.6(0.6–12.5)	1(16.7)	6(6.7)	0373	2.8(0.3–28)	5(12.5)	9(5.9)	0.174	2.3(0.7–7.2)
Aortic aneurysm, *N* (%)		0(0)	1(3.6)	1(1.6)	0.779	1(2.9)	1(1.6)	> 0.999	1.8(0.1–30.5)	0(0)	2(2.2)	> 0.999	––	1(2.5)	3(2)	> 0.999	1.3(0.1–12.6)
Cardiac involvement, *N* (%)		0(0)	1(3.6)	0(0)	0.293	1(2.9)	0(0)	0.354	__	0(0)	1(1.1)	> 0.999	––	1(2.5)	1(0.7)	0.374	3.9(0.2–63.3)
Disease severity	Mild, *N* (%)	0(0)	1(3.6)	4(6.5)	0.470	1(2.9)	4(6.5)	0.603	––	0(0)	5(5.6)	0.200	——	1(2.5)	9(5.9)	0.303	—
	Moderate, *N* (%)	2(33.3)	3(10.7)	6(9.7)		5(14.7)	6(9.7)			2(33.3)	9(10)			7(17.5)	15(9.9)		
	Severe, *N* (%)	4(66.7)	24(85.7)	52(83.9)		28(82.4)	52(83.9)			4(66.7)	76(84.4)			32(80)	128(84.2)		
Age at onset, years, median (IQR)		24(21–37)	25.5(23–32)	25(21–30)	0.861	25.5(22–32)	25(21–30)	0.589	––	24(21–37)	25(21–30)	0.909	––	25.5(21.5–32)	25(21–30)	0.617	—
Disease duration, years, median (IQR)		7.5(3–11)	9(6–14.5)	8.5(4–13)	0.778	8.5(6–14)	8.5(4–13)	0.594	––	7.5(3–11)	9(4–13)	0.802	––	8(5–13.5)	9(4–13)	0.734	—
Disease severity score, median (IQR)		7.5(6–9)	6(5–8.5)	6(5–8)	0.563	6(5–9)	6(5–8)	0.620	––	7.5(6–9)	6(5–8)	0.287	––	6(5–9)	6(5–8)	0.388	—

PTPN2 protein tyrosine phosphatase non-receptor type 2, *SNP* single nucleotide polymorphism, *N* number, *OR* odds ratio, *CI* confidence interval, *GIT* gastrointestinal. Comparisons were done using the chi-square tests for the qualitative variables and the Kruskal–Wallis or Mann–Whitney tests for the quantitative variables, as appropriate

Table 5 The relations between PTPN2 SNPs rs2542151 and rs7234029, and the different disease phenotypes

SNP				Musculoskeletal ($N=3$)	Ocular ($N=28$)	Neurological ($N=6$)	Peripheral vascular ($N=9$)	p value
PTPN2 rs2542151	Genotypes ($N=46$)		GG	0(0)	2(7.1)	1(16.7)	0(0)	0.900
			GT	1(33.3)	7(25)	1(16.7)	3(33.3)	
			TT	2(66.7)	19(67.9)	4(66.7)	6(66.7)	
	Models	Dominant ($N=46$)	GG + GT	1(33.3)	9(32.1)	2(33.3)	3(33.3)	
			TT	2(66.7)	19(67.9)	4(66.7)	6(66.7)	> 0.999
		Recessive ($N=46$)	GG	0(0)	2(7.1)	1(16.7)	0(0)	
			GT + TT	3(100)	26(92.9)	5(83.3)	9(100)	0.600
	Alleles ($N=92$)		G	1(16.7)	11(19.6)	3(25)	3(16.7)	
			T	5(83.3)	45(80.4)	9(75)	15(83.3)	0.950
PTPN2 rs7234029	Genotypes ($N=46$)		GG	0(0)	0(0)	1(16.7)	1(11.1)	0.081
			AG	0(0)	12(42.9)	0(0)	1(11.1)	
			AA	3(100)	16(57.1)	5(83.3)	7(77.8)	
	Models	Dominant ($N=46$)	GG + AG	0(0)	12(42.9)	1(16.7)	2(22.2)	0.270
			AA	3(100)	16(57.1)	5(83.3)	7(77.8)	
		Recessive ($N=46$)	GG	0(0)	0(0)	1(16.7)	1(11.1)	0.205
			AG + AA	3(100)	28(100)	5(83.3)	8(88.9)	
	Alleles ($N=92$)		G	0(0)	12(21.4)	2(16.7)	3(16.7)	
			A	6(100)	44(78.6)	10(83.3)	15(83.3)	0.626

PTPN2 protein tyrosine phosphatase non-receptor type 2, *SNP* single nucleotide polymorphism, *N* number. Comparisons were done using the chi-square tests

had a severe disease; and few patients had the gastrointestinal phenotype, reflecting the disease characteristics in Egypt [37]. Hence, further studies, particularly involving rs2542151 SNP as a potential genetic determinant of the disease, are recommended using a larger sample size and a broader disease spectrum to confirm the study results.

Conclusion

PTPN2 rs2542151 and rs7234029 SNPs do not seem to have associations with BD development, phenotypic expression, or severity in Egyptian patients. Further studies involving a larger sample size with variable clinical diversity are recommended to verify the results.

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Data availability Data of this work are available upon request.

Declarations

Ethics approval The study was approved by the Research Ethics Committee of the Faculty of Medicine, Cairo University (N-51–2023); and it conformed to the 1964 Helsinki Declaration and its subsequent revisions. Each subject provided an informed consent.

Disclosures None.

References

1. Bang DS, Oh SH, Lee KH, Lee ES, Lee SN (2003) Influence of sex on patients with Behçet's disease in Korea. J Korean Med Sci 18(2):231–235

2. Pineton de Chambrun M, Wechsler B, Geri G, Cacoub P, Saadoun D (2012) New insights into the pathogenesis of Behçet's disease. Autoimmunity Rev 11:687–98
3. Ideguchi H, Suda A, Takeno M, Ueda A, Ohno S, Ishigatsubo Y (2011) Behçet disease: evolution of clinical manifestations. Medicine (Baltimore) 90(2):125–132
4. Remmers EF, Cosan F, Kirino Y, Ombrello MJ, Abaci N, Satorius C et al (2010) Genomewide association study identifies variants in the MHC class I, IL10, and IL23RIL12RB2 regions associated with Behcet's disease. Nat Genet 42:698–702
5. Wu Z, Chen H, Sun F, Xu J, Zheng W, Li P et al (2014) PTPN2 rs1893217 single-nucleotide polymorphism is associated with risk of Behçet's disease in a Chinese Han population. Clin Exp Rheumatol 32(4 Suppl 84):S20–S26
6. Zhang Q, Li H, Hou S, Yu H, Su G, Deng B et al (2018) Association of genetic variations in PTPN2 and CD122 with ocular Behcet's disease. Br J Ophthalmol 102(7):996–1002
7. Wiede F, Shields BJ, Chew SH, van Vliet C, Galic S, Tremblay ML et al (2011) T cell protein tyrosine phosphatase attenuates T cell signaling to maintain tolerance in mice. J Clin Invest 121:4758–74
8. Scharl M, Paul G, Weber A, Jung BC, Docherty MJ, Hausmann M et al (2009) Protection of epithelial barrier function by the Crohn's disease associated gene protein tyrosine phosphatase n2. Gastroenterology 137(2030–40):e5
9. Long SA, Cerosaletti K, Wan JY, Ho JC, Tatum M, Wei S et al (2011) An autoimmune-associated variant in PTPN2 reveals an impairment of IL-2R signaling in CD4(+) T cells. Genes Immun 12:116–125
10. van Vliet C, Bukczynska PE, Puryer MA, Sadek CM, Shields BJ, Tremblay ML et al (2005) Selective regulation of tumor necrosis factor-induced Erk signaling by Src family kinases and the T cell protein tyrosine phosphatase. Nat Immunol 6:253–60
11. Wiede F, La Gruta NL, Tiganis T (2014) PTPN2 attenuates T-cell lymphopenia-induced proliferation. Nat Commun 5:3073
12. Zikherman J, Weiss A (2011) Unraveling the functional implications of GWAS: how T cell protein tyrosine phosphatase drives autoimmune disease. J Clin Invest 121:4618–4621
13. You-Ten KE, Muise ES, Itié A, Michaliszyn E, Wagner J, Jothy S et al (1997) Impaired bone marrow microenvironment and immune function in T cell protein tyrosine phosphatase-deficient mice. J Exp Med 186:683–693
14. Scharl M, Mwinyi J, Fischbeck A, Leucht K, Eloranta JJ, Arikkat J et al (2012) Crohn's disease-associated polymorphism within the PTPN2 gene affects muramyl-dipeptide-induced cytokine secretion and autophagy. Inflamm Bowel Dis 18:900–912
15. Spalinger MR, Kasper S, Chassard C, Raselli T, Frey-Wagner I, Gottier C et al (2015) PTPN2 controls differentiation of $CD4^+$ T cells and limits intestinal inflammation and intestinal dysbiosis. Mucosal Immunol 8:918–929
16. Wellcome Trust Case Control Consortium (2007) Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature 447(7145):661–678
17. Franke A, Balschun T, Karlsen TH, Hedderich J, May S, Lu T et al (2008) Replication of signals from recent studies of Crohn's disease identifies previously unknown disease loci for ulcerative colitis. Nat Genet 40:713–715
18. Zhang JX, He JH, Wang J, Song J, Lei HB, Wang J et al (2014) Associations between PTPN2 polymorphisms and susceptibility to ulcerative colitis and Crohn's disease: a meta-analysis. Inflamm Res 63(1):71–79
19. Thompson SD, Sudman M, Ramos PS, Marion MC, Ryan M, Tsoras M et al (2010) The susceptibility loci juvenile idiopathic arthritis shares with other autoimmune diseases extend to PTPN2, COG6, and ANGPT1. Arthritis Rheum 62:3265–3276
20. Okada Y, Terao C, Ikari K, Kochi Y, Ohmura K, Suzuki A et al (2012) Meta-analysis identifies nine new loci associated with rheumatoid arthritis in the Japanese population. Nat Genet 44:511–516
21. Hinks A, Cobb J, Sudman M, Eyre S, Martin P, Flynn E et al (2012) Investigation of rheumatoid arthritis susceptibility loci in juvenile idiopathic arthritis confirms high degree of overlap. Ann Rheum Dis 71:1117–1121
22. Smyth DJ, Plagnol V, Walker NM, Cooper JD, Downes K, Yang JH et al (2008) Shared and distinct genetic variants in type 1 diabetes and celiac disease. N Engl J Med 359:2767–2777
23. Espino-Paisan L, de la Calle H, Fernández-Arquero M, Figueredo MA, de la Concha EG, Urcelay E et al (2011) A polymorphism in PTPN2 gene is associated with an earlier onset of type 1 diabetes. Immunogenetics 63:255–258
24. Steck AK, Wong R, Wagner B, Johnson K, Liu E, Romanos J et al (2012) Effects of non-HLA gene polymorphisms on development of islet autoimmunity and type 1 diabetes in a population with high-risk HLA-DR, DQ genotypes. Diabetes 61:753–8
25. Plagnol V, Howson JM, Smyth DJ, Walker N, Hafler JP, Wallace C et al (2011) Genome-wide association analysis of autoantibody positivity in type 1 diabetes cases. PLoS Genet 7:e1002216
26. Barrett JC, Clayton DG, Concannon P, Akolkar B, Cooper JD, Erlich HA et al (2009) Genome-wide association study and meta-analysis find that over 40 loci affect risk of type 1 diabetes. Nat Genet 41:703–707
27. Yazısız V (2014) Similarities and differences between Behçet's disease and Crohn's disease. World J Gastrointest Pathophysiol 5(3):228–238
28. Valenti S, Gallizzi R, De Vivo D, Romano C (2017) Intestinal Behçet and Crohn's disease: two sides of the same coin. Pediatr Rheumatol Online J 15(1):33
29. Kim DH, Cheon JH (2016) Intestinal Behçet's disease: a true inflammatory bowel disease or merely an intestinal complication of systemic vasculitis? Yonsei Med J 57(1):22–32
30. Juárez-Melchor D, Munguía-Realpozo P, Mendoza-Pinto C, Etchegaray-Morales I, Ayón-Aguilar J, Mendez-Martínez S et al (2022) Genetic component of autoimmune rheumatological diseases. Reumatología Clínica 18(10):614–620
31. Barturen G, Beretta L, Cervera R, Van Vollenhoven R, Alarcón-Riquelme ME (2018) Moving towards a molecular taxonomy of autoimmune rheumatic diseases. Nat Rev Rheumatol 14(2):75–93
32. Davatchi F, Schirmer M, Zouboulis C, Assad-Khalil S, and Calamia KT, on behalf International Team for the Revision of the International Criteria for Behcet′s Disease (2007) Evaluation and revision of the international study group criteria for Behçet′s Disease. In: Proceedings of the American College of Rheumatology Meeting, November 2007, Boston, Mass, USA, abstract 1233.
33. Yosipovitch G, Shohat B, Bshara J, Wysenbeek A, Weinberger A (1995) Elevated serum interleukin 1 receptors and interleukin 1B in patients with Behcet's disease: correlations with disease activity and severity. Isr J Med Sci 31:345–348
34. Krause I, Mader R, Sulkes J, Paul M, Uziel Y, Adawi M et al (2001) Behçet's disease in Israel: the influence of ethnic origin on disease expression and severity. J Rheumatol 28:1033–6
35. Chan YH (2003) Biostatistics102: quantitative data – parametric & non-parametric tests. Singapore Med J 44(8):391–396
36. Chan YH (2003) Biostatistics 103: qualitative data –tests of independence. Singapore Med J 44(10):498–503
37. Attia DHS, Abdel Noor RA (2020) Severe Behçet's disease equally affects both genders in Egyptian patients: a multicentre retrospective follow-up study. Reumatismo 71(4):218–225

Authors and Affiliations

Doaa H. S. Attia[1] · Marwa Alkaffas[2] · Mervat Eissa[1] · Laila Rashed[2] · Rasha A. M. Khattab[3] · Radwa Elzanaty[4] · Rabab A. Khattab[5] · Lamees A. Samy[6]

✉ Doaa H. S. Attia
doaahassan@kasralainy.edu.eg

Marwa Alkaffas
madho_taal@yahoo.com

Mervat Eissa
mervateissa@kasralainy.edu.eg

Laila Rashed
lailarashed@kasralainy.edu.eg

Rasha A. M. Khattab
rashaabdelrazek@med.bsu.edu.eg

Radwa Elzanaty
elzanaty.radwa@kasralainy.edu.eg

Rabab A. Khattab
khattab.abab.mvupgo@gmail.com

Lamees A. Samy
dr.lamees.samy@hotmail.com

1 Rheumatology and Rehabilitation Department, Faculty of Medicine, Cairo University Hospitals, Saray El Manial Street, El Manial, Cairo 11956, Egypt

2 Medical Biochemistry and Molecular Biology Department, Faculty of Medicine, Cairo University, Saray El Manial Street, El Manial, Cairo 11956, Egypt

3 Clinical and Chemical Pathology Department, Faculty of Medicine, Beni-Suef University, Beni-Suef, Egypt

4 Ophthalmology Department, Faculty of Medicine, Cairo University, Saray El Manial Street, El Manial, Cairo 11956, Egypt

5 Ophthalmology Department, Helwan University Student's Hospital, Cairo, Egypt

6 Clinical and Chemical Pathology Department, Faculty of Medicine, Cairo University Hospitals, Saray El Manial Street, El Manial, Cairo 11956, Egypt