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ABSTRACT ASSOCIATION BETWEEN GENETIC VARIANTS OF SINGLE NUCLEOTIDE POLYMORPHISMS OF THE DISCOIDIN DOMAIN RECEPTOR TYROSINE KINASE 1 (DDR1) A/C (RS 2267641) AND GRANZYME B (GZMB) C/T (RS8192917) GENES IN VITILIGO

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ABSTRACT

Vitiligo manifests as advanced loss of melanocytes with reduced cellular adhesion. Discoidin Domain Receptor Tyrosine kinase1 (DDR1) is a main element affecting cellular adhesiveness associated with vitiligo. Granzyme B (GZMB) has significant role in cytotoxic T-cell induced apoptosis. This study aimed to evaluate the association between genetic variants of single nucleotide polymorphisms of DDR1 A/C (rs 2267641) and GZMB C/T (rs8192917) and the risk of developing vitiligo. The genotypes were investigated using allele discrimination assay comparing 120 patients having non-segmental vitiligo and 100 age and gender matched healthy individuals. We detected a significant prevalence of the CC genotype and C allele of both DDR1 and GZMB polymorphisms in vitiligo patients with early onset and progressive course compared to controls. Our results

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concluded that DDR1 A/C (rs 2267641) and GZMB C/T (rs8192917) polymorphisms may be risk factors for vitiligo.

Key words: Vitiligo, polymorphism, DDR1, GZMB

INTRODUCTION

Vitiligo is a complicated disease manifested by advanced degeneration and loss of melanocytes resulting in presence of white depigmented spots within the skin and affects nearly 1% of the population globally **(Gupta et al., 2019).** Various theories have been suggested for its progression, involving autoimmunity **(Ezzedine et al., 2015)**, cytotoxicity, genetic and molecular factors and enhancement of oxidative stress, which may lead to melanocyte degeneration **(Shi et al., 2016).** The loss of melanocytes seems to be related to alterations in cell adhesion **(Wagner et al., 2015).** Domain Receptor Tyrosine kinase 1 (DDR1) is a transmembrane tyrosine kinase receptor which establishes a multiplex with another transmembrane protein called E-cadherin. E-cadherin presents at cell junctions facilitating solid cell to cell adhesion, and DDR1 plays a significant role in maintaining E-cadherin and its mediated cellular assembly **(Eswaramoorthy et al., 2010)**. Vitiligo is likewise manifested by autoimmune destruction of melanocytes via cytotoxic T-cells within the skin **(Ferrara et al., 2013).** Granzyme B (GZMB) is an enzyme that plays significant role in cytotoxic T-cells triggered apoptosis **(Xu et al., 2018).**

Cytotoxic T cells prompt the stimulation of caspase-3 in a process that necessitates GZMB. Therefore, GZMB may cause apoptosis by initiating at least one of these caspases **(Thomas et al., 2000)**. In this

current study, we meant to evaluate the association between genetic variants at single nucleotide polymorphisms (SNPs) DDR1 A/C (rs 2267641) and GZMB C/T (rs8192917) genes and the risk of developing vitiligo.

MATERIALS AND METHODS

This work was conducted in association with the Medical Biochemistry & Molecular biology, Dermatology, Andrology & Sexually Transmitted Diseases (STDs) and Clinical Pathology Departments, Faculty of Medicine, Menoufia University from July 2018 to May 2019. This analysis involved 220 participants arranged into two groups: **Group 1** enrolled 120 patients having non-segmental vitiligo, selected from the Dermatology Outpatient Clinic, Menoufia University Hospitals. **Group 2** enrolled 100 ages and gender matched healthy individuals. All participants signed an informed consent before starting this work that is approved by The Local Ethics & Human Rights committee in Research at Faculty of Medicine, Menoufia University.

All sharers have been subjected to history taking, general and dermatological examinations and genotyping of DDR1 A/C (rs 2267641) and GZMB C/T (rs8192917) genes

Demographics data (age and gender) as well as the clinical variables of patients {age of onset, course, disease duration, presence of koebnerization, occurrence of leukotrichia, presence of spontaneous pigmentation, mucosal affection and family history} were recorded. Vitiligo was clinically categorized according to Taieb A and Picardo, 2007 **(Taïeb & Picardo, 2007)**. Selected cases of vitiligo were either

recently diagnosed without history of preceding treatment or old cases with totally depigmented lesions. Evaluation of disease activity was performed based on the Vitiligo Disease Activity (VIDA) score and assessment of disease severity was performed according to the Vitiligo Area Severity Index (VASI) score **(Bhor & Pande, 2006).** Any patient with vitiligo associated with any other inflammatory or autoimmune disease was excluded from our analysis.

DDR1 A/C (rs 2267641) and GZMB C/T (rs8192917) genotyping

Three milliliters of blood was acquired from all participants into an EDTA coated vacutainer for genomic DNA isolation using a Gene JET Whole Blood Genomic DNA Purification Mini extraction Kit **(Thermo Fisher Scientific, USA)** according to the manufacturer's directions. The quality of isolated DNA was assessed by a nano-drop then kept at -20°C until analysis.

TaqMan genotyping and allelic discrimination assay kits were applied for sample analysis utilizing the 7500 Real-time PCR system **(Applied Biosystems, Foster City, CA, USA)**. The provided fluorescent labeled TaqMan probes were sequenced as: *AGATCATGTCGAGGCTCAAGGACCC**[A/C]**AACATCATTCGG CTGCTGGGCGTGT for DDRI A/C (rs 2267641) (VIC dye for allele A and FAM dye for allele C)

*AGCAGCTGTCAGCACGAAGTCGTCT**[C/T]**GTATCAGGAAGC CACCGCACCTCTT for GZMB C/T (rs8192917) (VIC dye for allele C and FAM dye for allele T).

To detect the selected SNPs, real-time PCR was set with a reaction volume of 20 µl using 10 µl of TaqMan Genotyping Master Mix, 1.25

µl of 20X SNP assay mixture of probes and primers, 3.75 µl of nuclease-free water, and 5 µl of the extracted DNA. The reaction was completed in 96-well plates and proceeded as described: 50ºC for 1 minute (pre-PCR read), followed by 10 minutes at 95 ºC then 45 cycles of 15 seconds for denaturation at 94°C, 60 seconds for primer annealing at 50°C and 2 minutes for extension at 72°C and 1 minute at 60ºC for post-PCR

Statistical Analysis

Data were analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). To compare between groups for categorical variables, we used Chi-square test (Fisher or Monte Carlo). Student t-test was used for normally distributed quantitative variables while ANOVA was used to compare the three classified polymorphisms. Kruskal Wallis test was used for abnormally distributed quantitative variables. The significance of the results was referred to $P \leq 0.05$.

RESULTS

Regarding the SNPs and allele distribution, the genotype frequencies of the DDR1 A/C (rs 2267641) and GZMB C/T (rs8192917) polymorphisms were consistent with the Hardy-Weinberg equilibrium (HWE). In comparing the two groups, patients with vitiligo had the highest prevalence of the CC genotype and C allele of both DDR1 A/C rs2267641 [CC genotype 54(45%) and C allele 154(64.2%)] and GZMB C/T rs8192917 [CC genotype 49(40.8%) and C allele 146(60.8%)] gene variants compared to controls. Interpreting the risk association of the selected genes with the development of vitiligo, the

CC and AC genotypes of DDR1 (rs 2267641) were considered risk factors for vitiligo with OR 4.664*[95% CI: 2.24 – 9.71] and OR 2.185*[95% CI: 1.10 – 4.34], respectively. Moreover, the C allele compared to the A allele had OR 2.473* [95% CI: 1.68 – 3.63]. Regarding the GZMB, the CC and CT genotypes demonstrated a risk for developing vitiligo with OR 4.373*[95% CI: 2.09 – 9.16] and OR 1.938*[95% CI: 1.0 – 3.75], respectively and the C allele had OR 2.330*[95% CI: 1.59 – 3.42] versus the T allele **(Table 1).**

The results of the relationship of the examined genes with various parameters in patients with vitiligo revealed that the DDR1 A/C genotypes were significantly different regarding the onset of disease, disease course, age of onset, family history of autoimmune disease, type of vitiligo, spontaneous repigmentation, koebnerization , mucosal affection and presence of leukotrichia . The CC genotype was associated with an elevated VIDA score (score 3: 21 (38.9%) patients and score 4:18 (33.3%) patients). Additionally, the CC genotype had the highest percentage of VASI score. There was no significant variation between genotypes regarding age, gender or family history of vitiligo **(Table 2).**

Regarding GZMB C/T, there were significant variations between genotypes related to gender, family history of autoimmune disease, type of vitiligo, spontaneous repigmentation, koebnerization , mucosal affection and presence of leukotrichia .The CC genotype was associated with an elevated VIDA score (score 3: 23 (46.9%) patients and score4:18 (36.7%) patients). Moreover, the CC genotype had the highest percentage of VASI score. There was not any significant

variation among genotypes regarding age, age of onset, disease course or family history **(Table 3).**

Patients with vitiligo were stratified into subgroups based on: age of onset, course of the disease and family history of other autoimmune disease. The frequency of DDR1 CC genotype and C allele was statistically elevated in early onset vitiligo, progressive course and in negative family history of other autoimmune disease. For the GZMB gene, the CC genotype and C allele were statistically prevalent in early onset, progressive course and in positive family history of autoimmune disease **(Table 4)**.

RESULTS

Table (1): Comparison between both studied groups considering different parameters

	Patients (n= 120)	**Controls (n= 100)**	**Test Sig.**	**P value**		
Age(years) Median (Min-Max) Mean± SD	30 (12 - 65) 33.3 ± 16.6	32.5 (17-63) 33.8± 11.7	t=0.286	0.775		
Gender Male Female	**n (%)** 50(41.7%) 70(58.3%)	**n (%)** 46(46%) 54(54%)	χ^2=0.416	0.519		
DDR1 A/C rs 2267641	**n (%)**	**n (%)**			**OR**	**95 % C.I**
AA®	20(16.7%)	38(38%)	χ^2=17.807*	<0.001*	1.000	
AC	46(38.3%)	40(40%)			2.185*	1.10-4.34
CC	54(45%)	22(22%)			4.664*	2.24-9.71
Hardy-Weinberg equilibrium (HWE)	**χ^2=3.323 P=0.068**	**χ^2=3.203 P= 0.073**				
Allele	**n (%)**	**n (%)**				
A®	86(35.8%)	116(58%)	χ^2=21.586*	<0.001*	1.000	
C	154(64.2%)	84(42%)			2.473*	1.68-3.63
GZMB C/T rs8192917	**n (%)**	**n (%)**				
CC	49(40.8%)	19(19%)	χ^2=16.079*	<0.001*	4.373*	2.09-9.16
CT	48(40%)	42(42%)			1.938*	1.0- 3.75
TT®	23(19.249	39(39%)			1.000	
Hardy-Weinberg equilibrium (HWE)	**χ^2=3.095 P=0.078**	**χ^2=1.562 P= 0.211**				
Allele	**n (%)**	**n (%)**				
T®	94(39.2%)	120(60%)	χ^2=18.953*	<0.001*	1.000	
C	146(60.8%)	80(40%)			2.330*	1.59-3.42

χ^2: Chi square t: Student t-test *: Statistically significant ($p \leq 0.05$)

Table (2): Relationship between the genotypes of the DDR1 gene and different parameters in patient groups (n= 120)

	DDR1genotypes AA (n = 20)	 AC (n = 46)	 CC (n = 54)	Test of Sig.	P value
Age (years) Median (Min - Max) Mean ± SD	29 (13 – 63) 32.7 ± 15.5	27 (12 – 65) 32.7 ± 17.7	32 (12 – 63) 34.1 ± 16.3	F=0.108	0.898
	n (%)	n (%)	n (%)		
Gender Male Female	7 (35%) 13 (65%)	19 (41.3%) 27 (58.7%)	24 (44.4%) 30 (55.6%)	χ^2= 0.540	0.764
Onset Gradual Sudden	11 (55%) 9 (45%)	39 (84.8%) 7 (15.2%)	36 (66.7%) 18 (33.3%)	χ^2=7.298*	0.026*
Course Stationary Progressive	13 (65%) 7 (35%)	18 (39.1%) 28 (60.9%)	6 (11.1%) 48 (88.9%)	χ^2=22.281*	<0.001*
Age onset Late >20 years Early≤20 years	18 (90%) 2 (10%)	31 (67.4%) 15 (32.6%)	20 (37%) 34 (63%)	χ^2=19.739	<0.001*
Family history of vitiligo Negative Positive	15 (75%) 5 (20%)	33 (71.7%) 13 (28.3%)	48 (88.9%) 6 (11.1%)	χ^2=4.941	0.085
Family history of other autoimmune Negative Positive	4(20%) 16(80%)	34(73.9%) 12(26.1%)	35(64.8%) 19(35.2%)	$\chi^{2=}$17.658*	<0.001*
Type Generalized Acrofacial Focal	3 (15%) 6 (30%) 11 (55%)	12 (26.1%) 14 (30.4%) 20 (43.5%)	24 (44.4%) 22 (40.7%) 8 (14.8%)	χ^2=15.780*	0.003*
Koebnerization Absent Present	17 (85%) 3 (15%)	35 (76.1%) 11 (23.9%)	25 (46.3%) 29 (53.7%)	χ^2=14.118*	0.001*
Spontaneous repigmentation Absent Present	15 (75%) 5 (25%)	37 (80.4%) 9 (19.6%)	52 (96.3%) 2 (3.7%)	χ^2= 8.235*	0.016*
Mucosal affection Absent Present	20 (100%) 0 (0%)	43 (93.5%) 3 (6.5%)	41 (75.9%) 13 (24.1%)	χ^2=10.315*	0.006*
Leucotrichia Absent Present	18 (90%) 2 (10%)	45 (97.8%) 1 (2.2%)	43 (79.6%) 11 (20.4%)	χ^2=8.046*	0.018*
VIDA 1- 0 1 2 3 4	5 (25%) 8 (40%) 0 (0%) 4 (20%) 1 (5%) 2 (10.0%)	6 (13%) 8 (17.4%) 2 (4.3%) 15 (32.6%) 11 (23.9%) 4 (8.7%)	0 (0%) 1 (1.9%) 7 (13%) 7 (13%) 21 (38.9%) 18 (33.3%)	χ^2=49.899*	0.001*
VASI Median (Min – Max) Mean ± SD	10 (3 – 30) 10.9 ± 6.7	10 (3 – 35) 13.3 ± 9.4	20 (5 – 50) 21 ± 11.2	H=19.280*	<0.001*

χ^2:Chi square F:ANOVA H: Kruskal Wallis *:Statistically significant ($p \leq 0.05$)

Table (3): Relationship between the genotypes of the GZMB gene and different parameters in patient groups (n= 120)

	GZMB genotypes			Test of Sig.	P value
	TT (n = 23)	CT (n = 48)	CC (n = 49)		
Age (years) Median (Min - Max) Mean ± SD	 25 (13 – 63) 31.7 ± 16.1	 32 (12 – 65) 35 ± 18.3	 30 (12 – 57) 32.3 ± 15.1	F=0.443	0.643
	n (%)	n (%)	n (%)		
Gender Male Female	 5 (21.7%) 18 (78.3%)	 29 (60.4%) 19 (39.6%)	 16 (32.7%) 33 (67.3%)	χ^2=12.339*	0.002*
Onset Gradual Sudden	 18 (78.3%) 5 (21.7%)	 37 (77.1%) 11 (22.9%)	 31 (63.3%) 18 (36.7%)	χ^2=2.889	0.236
Course Stationary Progressive	 8 (34.8%) 15 (65.2%)	 19 (39.6%) 29 (60.4%)	 10 (20.4%) 39 (79.6%)	χ^2=4.389	0.111
Age onset Late >20 years Early≤20 years	 15 (65.2%) 8 (34.8%)	 31 (64.6%) 17 (35.4%)	 23 (46.9%) 26 (53.1%)	χ^2=3.783	0.151
Family history of vitiligo Negative Positive	 19 (82.6%) 4 (17.4%)	 36 (75%) 12 (25%)	 41 (87.8%) 8 (12.2%)	χ^2=1.261	0.532
Family history of other autoimmune Negative Positive	 21(91%) 2(13%)	 31(64.6%) 17(35.4%)	 21(42.9%) 28(57.1%)	χ^2=15.829*	0.001*
Type Generalized Acrofacial Focal	 0 (0%) 16 (69.6%) 7 (30.4%)	 15 (31.3%) 13 (27.1%) 20 (41.7%)	 24 (49%) 13 (26.5%) 12 (24.5%)	χ^2= 23.546*	<0.001*
Koebnerization Absent Present	 11 (47.8%) 12 (52.2%)	 38 (79.2%) 10 (20.8%)	 28 (57.1%) 21 (42.9%)	χ^2=8.419*	0.015*
Spontaneous repigmentation Absent Present	 20 (87%) 3 (13%)	 37 (77.1%) 11 (22.9%)	 47 (95.9%) 2 (4.1%)	χ^2=7.446*	0.024*
Mucosal affection Absent Present	 23 (100%) 0 (0%)	 43 (89.6%) 5 (10.4%)	 38 (77.6%) 11 (22.4%)	χ^2= 7.415*	0.025*
Leucotrichia Absent Present	 20 (87%) 3 (13%)	 47 (97.9%) 1 (2.1%)	 39 (79.6%) 10 (20.4%)	χ^2= 7.953*	0.019*
VIDA 1- 0 1 2 3 4	 5 (21.7%) 9 (39.1%) 0 (0%) 5 (21.7%) 4 (17.4%) 0 (0%)	 6 (12.5%) 8 (16.7%) 5 (10.4%) 17 (35.4%) 6 (12.5%) 6 (12.5%)	 0 (0%) 0 (0%) 4 (8.2%) 4 (8.2%) 23 (46.9%) 18 (36.7%)	χ^2= 63.002*	<0.001*
VASI Median (Min – Max) Mean ± SD	 10 (3 – 25) 10 ± 7.7	 10 (3 – 50) 16.3 ± 12.2	 20 (5 – 35) 19.4 ± 9.2	H= 16.959*	<0.001*

χ^2: Chi square F: ANOVA H: Kruskal Wallis *: Statistically significant (p value ≤ 0.05)

Table (4): Comparison between the genotype frequencies of the studied genes in control and vitiligo patients after stratification

	Control (n= 100)	Early onset ≤20 years (n= 51)	Late onset >20 years (n= 69)	Stationary Course (n= 37)	Progressive Course (n= 83)	Positive family history of other autoimmune disease (n= 47)	Negative family history of other autoimmune disease (n= 73)
DDR1							
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
AA®	38(38%)	2(3.9%)	18(26.1%)	13(35.1%)	7(8.4%)	16(34%)	4(5.5%)
AC	40(40%)	15(29.4%)	31(44.9%)	18(48.6%)	28(33.7%)	12(25.5%)	34(46.6%)
CC	22(22%)	34(66.7%)	20(29%)	6(16.2%)	48(57.8%)	19(40.4%)	35(47.9%)
χ^2 (P)		34.016* (<0.001*)	2.786 (0.248)	0.979 (0.613)	34.016* (<0.001*)	5.920 (0.052)	27.429* (<0.001*)
Allele							
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
A	116(58%)	19(20.2%)	67(48.6%)	44(59.5%)	44(59.3%)	44(46.8%)	42(28.8%)
C	84(42%)	83(79.8%)	71(51.4%)	30(40.5%)	124(74.7%)	50(53.2%)	104(71.2%)
χ^2 (P)		42.362* (<0.001*)	2.937 (0.087)	0.047 (0.828)	39.533* (<0.001*)	3.229 (0.072)	29.066* (<0.001*)
GZMB							
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
TT®	39(39%)	8(15.7%)	15(21.7%)	8(20.1%)	15(18.1%)	2(4.3%)	21(28.8%)
CT	42(42%)	17(33.3%)	31(44.9%)	19(51.4%)	29(34.9%)	17(36.2%)	31(42.5%)
CC	19(19%)	26(51%)	23(33.3%)	10(27%)	39(47%)	28(59.6%)	21(28.8%)
χ^2 (P)		18.138* (<0.001*)	7.263* (0.026*)	3.730 (0.155)	18.524* (<0.001*)	30.572* (<0.001*)	3.017 (0.221)
Allele							
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
T	120(60%)	33(32.4%)	61(44.2%)	35(47.3%)	59(35.5%)	21(22.3%)	73(50%)
C	80(40%)	69(67.6%)	77(55.8%)	39(52.7%)	107(64.5%)	73(77.7%)	73(50%)
χ^2 (P)		20.657* (<0.001*)	8.192* (0.004*)	3.548 (0.060)	21.715* (<0.001*)	36.337* (<0.001*)	3.421 (0.064)

χ^2: Chi square *: Statistically significant (p value ≤ 0.05)

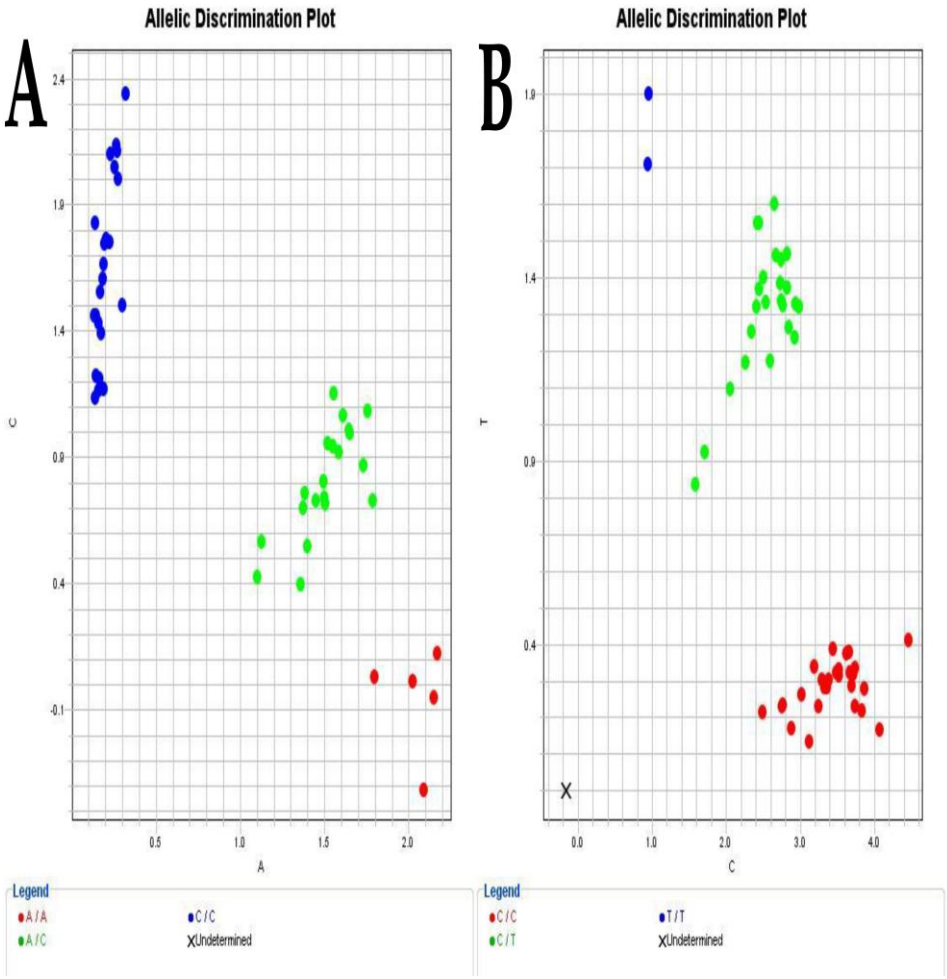

Fig. 1: A Allelic discrimination plot showing different genotypes of DDR1 A/C (rs 2267641). **B** Allelic discrimination plot showing different genotypes of GZMB C/T (rs8192917 genes.

DISCUSSION

Vitiligo is a multi-factorial disorder.The interactions of various etiological factors, including genetic risk factors, participate in the development and the pathological process of vitiligo **(Gupta et al., 2019).**The reduced adhesiveness of melanocytes to the adjacent

keratinocytes enhances their loss, which is a vital process in vitiligo pathogenesis (**Su et al., 2019)**. DDR1 is a main element affecting cellular adhesiveness associated with vitiligo (**Elgarhy et al., 2016)**.

In this current study, we aimed to evaluate the association between genetic variants of DDR1 A/C (rs 2267641) and GZMB C/T (rs8192917) genes and the risk of developing vitiligo. In this exploration, we detected a significant prevalence of the CC genotype and C allele of both DDR1 A/C rs2267641 and GZMB C/T rs8192917 polymorphisms in patients with vitiligo, which were also associated with increased risk of developing vitiligo. Additionally, the DDR1 CC genotype and C allele were statistically elevated in early onset vitiligo, progressive course and negative family history of other autoimmune disease groups versus controls. For the GZMB gene, the CC genotype and C allele were statistically prevalent in early and late onset vitiligo, progressive course and in positive family history of other autoimmune disease groups versus controls. Consistent with our findings, **Almasi-Nasrabadi et al., 2019** detailed an increased frequency of the DDR1 CC genotype in vitiligo patients compared to controls with a positive relationship between the C allele and the risk of vitiligo on Iranian populations. These findings were confirmed by **Silva De Castro et al., 2010** in a previous Brazilian study. These findings could be explained as vitiligo thought to occur due to melanocyte loss from the skin and other pigmented areas **(Zhang et al., 2005),** and the decreased expression of the primary proteins responsible for attachment of melanocytes to the basal layer of the epidermis, such as DDR1, has been considered as one of the main factors involved in

melanocyte loss **(Reichert-Faria et al., 2013).** Additionally, DDR1 has a significant role in cellular adhesion, migration and invasion and the expression of DDR1 may change the morphology of endogenous collagen fiber morphology **(Flynn et al., 2010)**. The DDR1 protein is considered a potent coordinator to collagen IV, which explains the fragile binding of melanocytes via DDR1 to the basement membrane and the increased liability of separation under pressure **(Cario, 2018)**. Consistent with our results, **Almasi-Nasrabadi et al., 2019** identified a predominance of the DDR1 CC genotypes in both early age onset and patients with no family history of autoimmune disease and **Silva de Castro et al., 2010** reported that the risk of developing vitiligo was age dependent**.** Similar to our results, **Xu et al., 2018** in a study conducted on a Chinese Han population, showed that the GZMB C/T (rs8192917) polymorphism, out of 15 other polymorphisms of GZMB, was significantly associated with vitiligo and the C allele had an elevated risk of vitiligo**. Ferrara et al. 2013** specified a main association of generalized vitiligo with the haplotype comprised of rs8192917-C—rs11539752-C of GZMB. GZMB protein is an enzyme that plays a major role in cytotoxic T cell induced apoptosis **(Xu et al., 2018)**. Cytotoxic T cells are thought to have a vital role in processes of melanocyte loss and degeneration. Cytotoxic T cells can precisely identify melanocytes, and their level in the circulation of vitiligo patients is considerably elevated, especially in progressive stages **(Lv et al., 2019)**. This finding goes ahead with our results of an increased frequency of CC genotype in progressive courses of vitiligo. Additionally, more GZMB-positive T-cells have been found in lesions

of autoimmune related skin diseases, like atopic dermatitis and psoriasis, compared to healthy skin **(Hussein et al, 2009)**. GZMB is associated with the cleavage of many auto antigens of systemic autoimmune disorders, and GZMB produced auto antigens have been identified in tissues of autoimmune disorders, such as systemic lupus erythematous and scleroderma **(Turner et al, 2019)**. This fact may explain our finding of a significant prevalence of the GZMB CC genotype and C allele in positive family history of autoimmune disease groups.

Conclusion

This study found that the CC variants of DDR1 A/C (rs 2267641) and GZMB C/T (rs8192917) polymorphisms may be risk factors for vitiligo and may be associated with aggressive clinical presentation.

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الملخص العربى

العلاقة بين المتغيرات الوراثية لأشكال النوكليوتيدات الفردية لجينات

(DDR1) A / C (rs 2267641 1) و GZMB) C / T (rs8192917 B

في مرض البهاق

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الطبية والبيولوجيا الجزيئية ، [٢]الأمراض الجلدية و الذكورة الحيوية أقسام [١]الكيمياء المنوفية والامراض المنتقلة بالاتصال الجنسي و [٣]الباثولوجيا الإكلينيكية كلية الطب- جامعة

البهاق هو مرض معقد يظهر كخسارة متقدمة في الخلايا الصباغية. أثبتت الأدلة الحديثة أيضًا وجود خلفية ذاتية المناعة للبهاق. مستقبِل الديسكودين تيروسين كيناز (DDR1)هو العنصر الرئيسي الذي يؤثر على الالتصاق الخلوي المصاحب للبهاق جرانزيم بي (GZMB) .هو إنزيم له دور مهم في موت الخلايا المبرمج. هدفت هذه الدراسة إلى تقييم العلاقة بين المتغيرات الوراثية لأشكال النوكليوتيدات الفردية (SNP) من DDR1 A / C (Rs 2267641)و GZMB C / T (rs8192917)وخطر الإصابة بالبهاق. تم التحقيق في الأنماط الجينية للجينات DDR1 A / C و GZMB C / T باستخدام اختبار التمييز أليل مع التفاعل التسلسلي لانزيم البوليمراز و مقارنة مائة وعشرون مريضا مع مائة من الأصحاء كمجموعة ضابطة. أظهرت نتائج الدراسة انتشارًا كبيرًا للنمط الوراثي CC وأليل Cلكل من الجينات DDR1 و GZMB في المرضى الذين يعانون من البهاق مقارنةً بالضوابط. خلصت نتائجنا إلى أن تعدد الأشكال الجينية (DDR1 A / C (rs 2267641 و GZMB C / T (rs8192917)قد تكون عوامل خطر للبهاق وقد تتوقع التطور المحتمل للمرض.