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ASSOCIATION OF INTERLEUKIN 1 RECEPTOR TYPE 1 POLYMORPHISM RS956730 WITH VITILIGO SUSCEPTIBILITY IN ASSIUT UNIVERSITY HOSPITALS.

Abdelrahman Elsayed[1], Salwa S.Ahmed[2], Mona H. Abdel-Rahim[2], Eman R. M. Hofny[3], Ragaa S. Rashwan[2]*

[1]*Department of Microbiology and Immunology, Faculty of Pharmacy, Assiut University, Assiut, Egypt*
[2]*Medical Microbiology and Immunology Department, Faculty of Medicine, Assiut University, Assiut, Egypt*
[3]*Department of Dermatology, Faculty of Medicine, Assiut University, Assiut, Egypt*

Background and aims*: Vitiligo, an autoimmune skin condition, largely resulted from genetic factor. Vitiligo is distinguished by white regions of skin that have lost the capacity to create pigment from melanocytes. IL-1 receptor (IL1R1) performs a vital function in the immunological and inflammatory responses triggered by various cytokines. It has been correlated with other disorders of the immunological system such as systemic lupus erythematous, inflammatory spondylitis and rheumatoid arthritis. This study aimed to evaluate the correlation of IL1R1 gene polymorphisms (rs956730) and vitiligo pathogenesis.* ***Patients and methods****: It was a case-control investigation which included 100 patients suffering from vitiligo, in addition to 100 apparently healthy individuals, recruited to the Dermatology Department, Assiut University, Egypt. The IL1R1 single nucleotide polymorphism (SNP) rs956730 was genotyped by RT-PCR.* ***Results****: The allele frequency in the SNP rs956730 shows a significant difference between vitiligo patients and healthy subjects. AA genotype was 65.0% among cases versus 25.0% among controls. So, carriers of AA genotype were at risk condition for vitiligo (OR = 8.03, p-value 0.001).* ***Conclusion****: The present study suggested that A allele of IL1R1 rs956730 is risk factor associated with the development of vitiligo.*

Key words*: Vitiligo, Interleukin 1 receptor type-1, SNP, Polymorphism, Real Time PCR*

INTRODUCTION

The skin condition vitiligo results in pigment loss. It is caused by the selective decline of melanocytes, which makes The coloring less noticeable within the affected areas[1] . Based on screening of over 50 international research, an updated study estimates that 0.5–2% of people worldwide suffer with vitiligo[2].Research indicates that vitiligo lesions on exposed or sensitive body parts, including the hands, face, or genitalia, are more harmful to a patient's overall health[3]. Melanocytes are particularly killed by adaptive immune activation in vitiligo. T lymphocytes are intermittently infiltrated next to melanocytes, especially in the forefront of vitiligo depigmentation[4]. A chalky white enlargement of depigmented skin is seen in Wood's lamp examination of vitiligo, although hypopigmented skin does not grow[5].

Both men and women are equally impacted, although few studies have found a female dominance, which might be related to the fact that women are more likely than men to suffer from autoimmune diseases or because women prioritize their appearance over all other factors when seeking help and therapy[6]. Most studies indicate that half of the population has symptoms before the age of 20,

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*Corresponding author: Ragaa Sedeik Rashwan, E-mail: ragaa.sedeik@aun.edu.eg

and vitiligo typically manifests before the age of thirty. A family history of the disease may be connected to a child's early development[7]. According to the Vitiligo Global Issues Consensus Conference's review between 2011 and 2012, vitiligo may appear clinically in three different forms. segmental, non-segmental, mixed/unclassified[8]. A clinician-reported measure called the Vitiligo Area Scoring Index (VASI) evaluates the degree of depigmentation and the affected body surface area[9]. Strong and pleiotropic, interleukin-1 (IL-1) is a proinflammatory mediator of congenital inflammation, immune defense, and immune-mediated diseases[10]. Interleukin 1 family include interleukin-1 receptor antagonist (IL1RA), interleukin-1 beta (IL1B), and interleukin-1 alpha (IL1A)[11]. Interleukin 1 type 1 receptor (IL1R1) is also known as CD121a (Cluster of Differentiation 121a)[12]. Different cell types, such as monocytes, activated macrophages, and endothelial cells, can produce IL-1[13].

IL1R1 gene encodes a cytokine receptor that is part of the interleukin-1 receptor family. This protein is responsive to interleukin-1 receptor antagonist (IL1RA), interleukin-1 beta (IL1B), and interleukin-1 alpha (IL1A). The broad proinflammatory action of IL-1 is explained by the expression of IL1R1 by the majority of immune and nonimmune cells[14]. In a region located on chromosome 2q12, *IL1R1* gene forms a cytokine receptor gene cluster with interleukin 1 receptor, type II (IL1R2), interleukin 1 receptor-like 2 (IL1RL2), and interleukin 1 receptor-like 1 (IL1RL1)[15].

SNPs can also be used to track the inheritance of disease-associated genetic variants within families[16]. Understanding IL1R1 polymorphisms may help identify individuals at risk for certain diseases. It may also inform treatment strategies, particularly in diseases where IL-1 signaling is a key regulatory component of the pathology[17].

Previous studies have linked IL1R1 genetic polymorphisms to a variety of inflammatory disorders, including atopic asthma, alcoholic liver disease, hematogenous osteomyelitis, invasive pneumococcal disease, and IgA nephropathy[18].

Xie, M., et al. showed that the *IL1R1* and *IL1R2* genes influence the cell metabolism and the response of immunological inflammation induced through numerous cytokines[19].

IL-1 regulates both coagulation and inflammation, hence a few research has linked SNPs in IL-1 to a variety of immunological disorders. For example, prior studies indicated that venous thrombosis risk was increased by the IL1B, IL1RA, IL1R1, and IL1R2 haplotypes and polymorphisms in the IL1/IL1Ra, CTLA-4, and Apo1/Fas genes are linked to IgA nephropathy[19]. Interleukin 1 receptor, type 1 (IL1R1) and Interleukin 1 receptor, type 2 (IL1R2) are cytokine receptors from the interleukin 1 receptor family. They play a crucial role in numerous inflammatory and immunological reactions triggered by cytokines[20]. The study performed in Menoufia in 2022 found significant differences in IL-1β levels in perilesional areas of vitiligo compared to lesional and control groups. This suggests that IL-1β has a role in the development and progression of active vitiligo[21].

There is no prior research associating IL1R1 to vitiligo susceptibility and severity. Accordingly, the current study's objective was to assess the correlation among gene polymorphism of the *IL1R1* gene (rs956730) and disease susceptibility in vitiligo sufferers.

MATERIALS AND METHODS

This case control study was carried out from August 2021 to September 2023 in the Department of Dermatology, Assiut University Hospitals. A total of one hundred vitiligo patients attended Dermatology clinic and were newly diagnosed as vitiligo. Their diagnosis is based on clinical examination and confirmed by Wood’s Lamp examination. Patients below 16 years old, or patients diagnosed with other skin disease (other than vitiligo) were excluded from the study. Informed consent from patients and controls was taken and ethical approval for this study was obtained from the Institutional review board (IRB) and the Ethical Committee of the Faculty of Medicine - Assiut University prior to study execution (on 5/7/2021 with IRB local approval number 04-2023-200328), according to the guidelines of the Declaration of Helsinki. The control group included 100 healthy individuals with no vitiligo, other skin diseases or systemic diseases that were ethnically and geographically matched with

patients[19,22]. For every research participant, demographic and clinical data (age, sex, history of vitiligo, duration, age at onset, location of first lesion, triggering factors, presence of other autoimmune diseases and vitiligo area and severity index) has been obtained.

DNA extraction and genotyping of IL1R1 (rs956730) assay

For every participant, 3ml of whole blood were collected in an EDTA tube for genomic DNA (gDNA) extraction, and centrifuged for 10 minutes at 1,500 rpm, then stored at -80°C. Genotyping of the IL1R1 (rs956730) have been done in the Medical Research Center of Faculty of Medicine, Assiut University using the 7500 Real-Time PCR Applied Biosystem, USA. Genotyping was performed according to the manufacturer's instructions. The technique was done in three main steps:

1. Extraction of genomic DNA: DNA was extracted using Thermofisher Scientific Gene JET™ Whole Blood Genomic DNA Purification Mini Kit (Waltham, Massachusetts, USA) in order to quickly and effectively extract high-quality genomic DNA from whole blood.
2. Amplification of the extracted DNA: The extracted DNA was amplified using TaqMan genotyping Master Mix (Thermo-Fisher Scientific, USA) and ready-made TaqMan SNP genotyping assay kit for IL1R1 rs956730 SNP.
3. Allelic discrimination (AD) by real time PCR: The real- time PCR instrument software plots the results of the AD data as a scatter plot of Allele A (VIC® dye) versus Allele G (FAM™ dye). On the plot, each well of the 96-well reaction plate is represented by a separate point as shown in **Fig. (1)**.

The **Fig.** displays amplification curves for vitiligo samples, with FAM dye on the X-axis (G allele) and VIC dye on the Y-axis (A allele). Curve is separated into four parts. The blue quarter is homozygous 2; the red circle is homozygous 1; the green triangle is heterozygous, and # symbol is negative.

Statistical investigation

With SPSS version 26, data analysis was done. The frequency and percentage representations of the categorical data were used. The study utilized the tools of the Chi square ($\chi 2$), independent Sample T test, One Way ANOVA, and Kruskal Wallis test. Using an online tool, the measured genotype frequencies were adjusted to the Hardy-Weinberg equilibrium[23] (https://wpcalc.com/en/equilibrium-hardy-weinberg). G Power software version 3.1.3 was used to compute the sample size, and the Z test was used to compare the differences between two proportions.

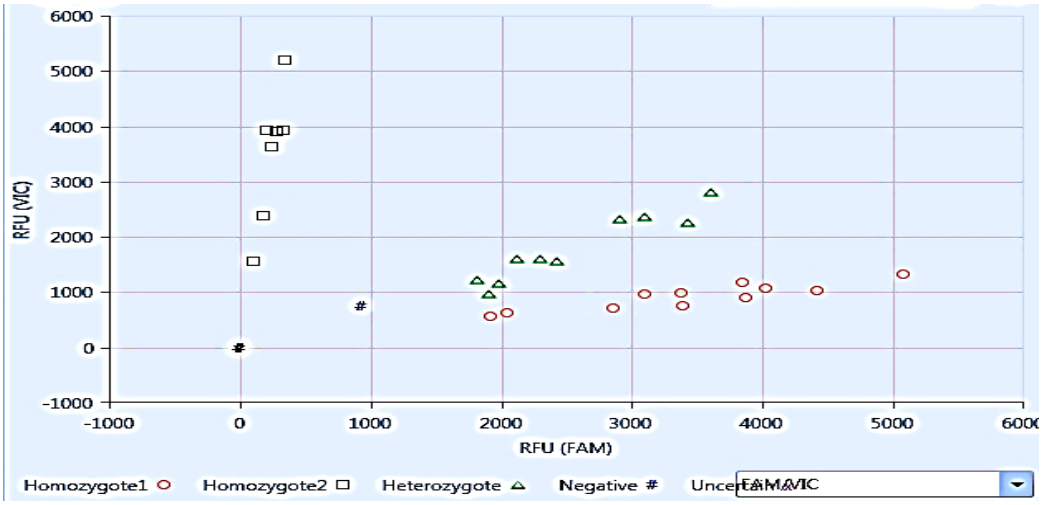

Fig.1: Allelic discrimination plot of some samples for rs956730.

RESULTS AND DISCUSSION

Demographic data of vitiligo patients and controls

The present study was conducted on 200 participants who were sub classed into two main groups: healthy control (n = 100) and vitiligo patients (n = 100). As shown in **Table 1,** the mean age of cases was 34.04 ±14.7, ranging from 16 to 90 years, while the mean age of controls was 44.90 ±18.0, ranging from 19 to 82 years (p-value = 0.001). In terms of gender, 37.0% of cases and 58.0% of controls were males, whereas 63.0% of cases and 42.0% of controls were females (p-value = 0.001).

Associations of allele and genotype frequencies with vitiligo risk

It was observed that there was a higher risk of contracting vitiligo among individuals with genotypes GA and AA. Moreover, AA and GG genotypes had the most positive (risky) and negative (protective) correlation with vitiligo, respectively. AA genotype was 65% among vitiligo cases compared to 25% among controls (OR=8.03), GA was 13% among vitiligo cases compared to 7% among controls (OR= 5.74), GG was 22.0% among vitiligo cases compared to 68.0% among controls. The allele frequency in the SNP rs956730 shows a significant difference between vitiligo patients and healthy subjects; the G allele was protective, and the A allele was a predisposing genetic element for vitiligo, (OR = 6.29, p-value 0.001), and the (A) allele was 71% versus (G) wild allele 28.5% among cases, as shown in **Table 2.**

Table 1 : Age and sex characteristics of vitiligo patients and controls.

Variables	Patients (N=100)	Controls (n=100)	P-value
Age (years)			
Mean ± SD (Range)	34.04±14.7 (16-90)	44.90±18.0 (19-82)	**<0.001**
Gender			
▪ Males	37 (37.0%)	58 (58.0%)	**0.001**
▪ Females	63 (63.0%)	42 (42.0%)	

Data is expressed as Mean ± SD (range), or frequency (%)

Table 2: Allele and genotype frequency distribution of SNP rs956730 among vitiligo patients and Controls.

rs956730 (G >A)	Patients (n=100)	Controls (n=100)	OR (95% CI)	Test value (χ^2)	P-Value^
Genotype					
▪ GG	22 (22.0%)	68 (68.0%)	**1.00**	**43.08**	**<0.001**
▪ AG	13 (13.0%)	7 (7.0%)	5.74 (2.03-16.19)		
▪ AA	65 (65.0%)	25 (25.0%)	8.03 (4.12-15.65)		
Dominant					
▪ GG	22 (22.0%)	68 (68.0%)	**1.00**	**42.74**	**<0.001**
▪ AA+AG	78 (78.0%)	32 (32.0%)	7.53 (4.00-14.18)		
Recessive					
▪ GG+AG	35 (35.0%)	75 (75.0%)	**1.00**	**32.32**	**<0.001**
▪ AA	65 (65.0%)	25 (25.0%)	5.57 (3.02-10.27)		
Alleles					
▪ G	57 (28.5%)	143 (71.5%)	**1.00**	**73.96**	**<0.001**
▪ A	143 (71.5%)	57 (28.5%)	6.29 (4.07-9.71)		

Distribution of SNP rs956730 among vitiligo patients regarding age and gender

There was no statistically significant difference between types of genotype distribution in SNP rs956730 among vitiligo patients regarding age, gender and, smoking as shown in **Table 3.** The mean age of patients with AA genotype was 35.08 ± 14.53, patients with GA genotype were 32.46 ± 13.38 and patients with GG genotype was 31.91±16.21. Regarding smoking, 89.2 % of AA, 76.9% GA, and 81.8% GG genotype respectively were non-smoker. Regarding gender, male vitiligo patients of genotypes AA, GA, and GG were 36.9%, 38.5%, and 36.4%, respectively. Female vitiligo patients of genotypes AA, GA, and GG were 63.1%, 61.5%, and 63.6%, respectively, as shown in **Table 3.** It was found that vitiligo incidence was higher in females of AA genotyping.

There was no statistically significant difference between different types of genotypes (AA, AG, GG) distribution of SNP rs956730 among vitiligo patients regarding, types of vitiligo, history of another autoimmune disease, presence of comorbidities and disease severity by VASI score. Median of VASI score was higher in GG genotyping (**Table 4)**.

Table 3: Association between SNP rs956730 and demographic data of vitiligo patients.

	rs956730 (G>A)			**P-Value**
	GG (n=22)	**AG (n=13)**	**AA (n=65)**	
Age: Mean ± SD	31.91±16.21	32.46±13.38	35.08±14.53	0.631^
Gender				
▪ Males	8 (36.4%)	5 (38.5%)	24 (36.9%)	0.992^^
▪ Females	14 (63.6%)	8 (61.5%)	41 (63.1%)	
Smoking				
▪ Smoker	4 (18.2%)	3 (23.1%)	7 (10.8%)	0.412^^
▪ Non-smoker	18 (81.8%)	10 (76.9%)	58 (89.2%)	

Table 4: Association between SNP rs956730 and other clinical data among patients with vitiligo.

	Rs956730 (G>A)			**P-Value***
	GG (n=22)	**AG (n=13)**	**AA (n=65)**	
Types of disease				
Non segmental				
▪ Generalized	14 (63.6%)	10 (76.9%)	42 (64.6%)	0.670^
▪ Acrofacial	1 (4.5%)	1 (7.7%)	8 (12.3%)	0.552^
▪ Focal	1 (4.5%)	0 (0.0%)	1 (1.5%)	0.588^
Segmental	5 (22.7%)	2 (15.4%)	10 (15.4%)	0.720^
Mixed	1 (4.5%)	0 (0.0%)	4 (6.2%)	0.645^
History of autoimmune	1 (4.5%)	3 (23.1%)	5 (7.7%)	0.149^
History of comorbidity	1 (4.5%)	3 (23.1%)	6 (9.2%)	0.198^
Disease severity/ Total VASI score				
Median (range)	2.02 (0.3-14.51)	1.50 (0.01-24.50)	1.30 (0.13-22.30)	0.722^^

Discussion

There is increasing evidence that cytokines are important in the depigmentation process of vitiligo. Cytokines, such as IL-1, interferon γ, and tumor necrosis factor alpha (TNF-α), which are released by lymphocytes and keratinocytes, can initiate apoptosis in melanocytes. Moreover, TNF-α, IL-1α, IL-6, and TGF-β are the potent inhibitors of melanocyte growth[24,25].

The biological activity of the multifunctional cytokine IL-1 is mediated by its receptors[26].

several studies reported that IL1R1 and IL1R2 gene polymorphisms had impacts on inflammation-related diseases. IL1R1 is an important mediator involved in many cytokine- induced immune and inflammatory responses[27]. Recently, some studies revealed that the expression of IL1R1 was observably increased in several bone disease[28,29,30,31], IBD[32,33], Rheumatoid Arthritis[34]. Therefore, we try to explore the relationship between IL1R1 and vitiligo risk.

To the best of our understanding, this is the first study to look at the connection between vitiligo and IL1R1 variation. Vitiligo is a complex disorder with a complex, multiple, and polygenic etiology. The interaction between heredity and environment commonly influences the development and course of vitiligo. These days, autoimmune response-influencing elements receive greater attention[34].

Patients with vitiligo had a greater frequency of anxiety, sleep disruption, depression, atopic dermatitis, and psoriasis. Sensorineural hearing loss, folate deficiencies, and glaucoma were among the other high-incidence comorbidities[35]. Numerous cutaneous and non-cutaneous autoimmune diseases are associated with vitiligo, especially in women and the elderly[36].

Recent research has demonstrated a connection between the IL1R1 polymorphism and the etiology and development of autoimmune disorders, including Inflammatory Bowel Disease with rs2058660[32], Systemic lupus erythematosus (SLE) with rs2234650[37], and rheumatoid arthritis (RA) with rs956730[34]. The present study found that the average age of vitiligo patients was 34.04 ±14.7 years, with a range of 16 to 90 years. These findings were consistent with the study, conducted in Brazil and included 669 patients with a mean age of 33.6 ±18.6 years (1-84).[38]

In our study, there was higher prevalence of vitiligo among females. This may be due to the stronger immune reactivity in females (63 %) than males (37 %) this may be due to the immune reactivity is stronger in females than in males with a sex ratio of around 2:1[39]. Parallel with our study, Zhang et al., show that rs956730 was associated with osteoporosis risk especially among females[40]. The current investigation revealed that those with genotype GA, AA had a greater chance of developing vitiligo. Regarding SNP rs956730, the allele frequency shows a significant difference between patients with vitiligo and healthy subjects. The G allele (dominant model) was protective, and the A allele was a predisposing genetic element for vitiligo (OR = 6.29). The A allele was 71.5% among cases versus 28.5% among controls. Rs956730 was risky which may be because these SNPs affect the expression of the *IL1R1* gene and eventually influence the activity of the inflammatory and immune reactions.

Concurrent with our study, a research on TB risk found that rs956730 AA (Minor Allele Frequency) allele was related with an elevated danger of effective inflammatory diseases including tuberculosis in the Chinese Han population[41]. In another studies, the role of SNPs of IL1R1 was investigated in lumbar disc herniation in Han population in northwest China. Furthermore, IL1R1 rs956730 (AA) was related to an increased risk of lumbar disc herniation based on the homozygous genotype AA in males[42]. Liu et al., demonstrated the correlation between rs956730 (MAF) and RA susceptibility in females in Chinese Han population (after stratification of gender and age)[34]. However, previous studies on IgA nephropathy[19], Coronary Artery Disease (CAD)[18], and on osteonecrosis of the femoral head (ONFH)[43] found that SNP rs956730 constructed for IL1R1 gene had no significant association with risk of these diseases. Contrary to our study, it was found that IL1R1 rs956730 both (GG and AA) allele were protective factors for ankylosing spondylitis[22]. This inconsistency may result from the geographical difference.

The highest prevalence of comorbid conditions and autoimmune disorders was seen in patients with AA genotyping of rs 956730, indicating a link between AA genotyping and these illnesses. AA genotyping of rs 956730 was greatest in generalized and segmental vitiligo, suggesting a connection between AA genotyping and these types of vitiligo.

Conclusion

The present study has shown a significant association between A (the mutant type) allele variant of IL1R1 rs956730 and vitiligo susceptibility. Therefore, rs956730 will be a potential therapeutic target and/or diagnostic/prognostic biomarker for determining the possibility of developing vitiligo. The small sample size (as it is only confined to 100 patients and 100 controls of study subjects) is considered a limitation to our study.

Nevertheless, there are limitations that need to be noticed. Our current research is not fundamental, and further functional studies and larger population-based prospective studies are required in order to understand the genetic factors underlying vitiligo.

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علاقة تعدد الأشكال الوراثية لجين مستقبل الإنترلوكين-١(rs956730) في مرضى البهاق بمستشفيات جامعة أسيوط

عبد الرحمن السيد أحمد[١] – سلوى سيد سيف الدين[٢] – إيمان رياض حفني[٣] – منى حسين محمد عبد الرحيم[٢] – رجاء صديق رشوان[٢]

[١] قسم الميكروبيولوجيا والمناعة ، كلية الصيدلة ، جامعة أسيوط، أسيوط ، مصر

[٢] قسم الميكروبيولوجيا الطبية والمناعة كلية الطب، جامعة أسيوط، أسيوط ، مصر

[٣] قسم الأمراض الجلدية كلية الطب ، جامعة أسيوط، أسيوط ، مصر

البهاق مرض جلدي ذاتي المناعي ، ينتج إلى حد كبير عن العامل الوراثي. يتميز البهاق بوجود مناطق بيضاء من الجلد فقدت القدرة على تكوين الصبغة من الخلايا الصباغية. يؤدي مستقبل IL-1 (IL1R1) وظيفة حيوية في الاستجابات المناعية والالتهابات الناجمة عن السيتوكينات المختلفة. وقد ارتبط مستقبل الإنترلوكين-١ باضطرابات أخرى في الجهاز المناعي مثل مرض الذئبة الحمراء والتهاب الفقارات العظمية والتهاب المفاصل الروماتويدي. هدفت هذه الدراسة إلى تقييم العلاقة بين تعدد أشكال الجينات (rs956730) IL1R1 والتسبب في حدوث مرض البهاق. هذا البحث عبارة عن دراسة وصفية للحالات المرضية و الأصحاء والتي شملت ١٠٠ مريض يعانون من البهاق، بالإضافة إلى ١٠٠ شخص من الأصحاء بقسم الأمراض الجلدية، جامعة أسيوط، مصر. تم التنميط الجيني لتعدد أشكال النوكليوتيدات المفردة IL1R1 (SNP) rs956730 بواسطة RT-PCR. يظهر تردد الأليل في SNP rs956730 يظهر فرقا كبيرا بين مرضى البهاق والأشخاص الأصحاء. كان الأليل AA موجود بنسبة ٦٥ % بين الحالات مقابل ٢٥% بين الأصحاء. لذلك، كان حاملو الأليل A أكثر عرضة لخطر الإصابة بالبهاق (معامل الخطورة = ٨.٠٣، القيمة الاحتمالية ٠.٠٠١). تشير الدراسة الحالية إلى أن الأليل A IL1R1 rs956730 هو عامل خطورة مرتبط بتطور البهاق.