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A Comparative Study of NLRP1 Gene for Iraqi Vitiligo Patients with 1000 Genomes

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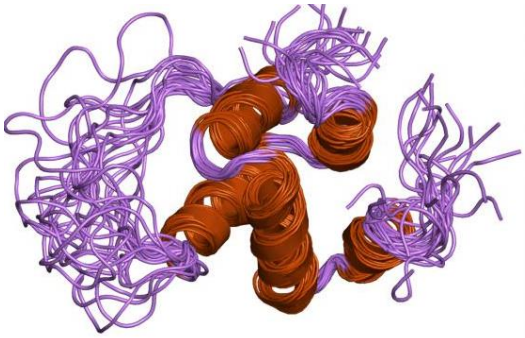
ABSTRACT

Generalized Vitiligo (GV) is a complicated disease with many factors that can influence its severity. The GV pathway and its severity are influenced by genetic, epigenetic deleted the comma, and environmental factors. Many genes have been identified at the genetic level that may be involved in this type of disease. As a result, the primary goal of this project is to investigate the impact of some SNPs in the promoter region of the NLRP1 gene. A total of 50 GV patients and 2504 healthy controls were recruited to see if single nucleotide polymorphisms (SNPs) in the NLRP1 gene (rs925595, rs925596, rs 925597, rs925598, rs11569898, rs2716936, rs79376273, rs1156990, rs8072203, and rs2670642) contribute to determine the relationship between GV and these SNPs, the data was statistically analyzed. Three SNPs (rs1156989, rs925595, and rs925597) showed a significant association with GV among ten tested SNPs. The three SNPs were found within a linkage disequilibrium block. Haplotypes H3, H8, H9, and H10 which included rs1156989, rs925595, and rs925597 were found to be associated with GV. The findings suggest that NLRP1 polymorphisms are linked to GV development.

GRAPHICAL ABSTRACT



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Introduction

Autoimmune diseases are a group of physiological disorders with highly diverse pathogenesis and clinical manifestations that affect more than 5% of the global population [1]. Vitiligo is a depigmenting skin disorder characterized by the selective loss of melanocytes, resulting in pigment dilution in the affected areas of the skin [2]. The disease is classified based on the distribution and location of white spots. The two most common types of vitiligo are segmental and non-segmental vitiligo and they are distinguished by the distribution of lesions on the skin [3]. Non-segmental vitiligo (GV), an acquired chronic depigmentation illness, is distinguished by symmetrical white patches on both sides of the body. Segmental vitiligo (SV) lesions are distinguished by their asymmetrical distribution and distinct dermatomes (skin areas supplied by individual spinal neurons) [4, 5]. Both men and women are affected, but women and girls are more likely to seek assistance due to the greater social impact on them [6, 2]. The majority of people develop NSV between the ages of 10 and 30, but it can occur at any age [2]. Significant progress has been made in our understanding of GV pathogenesis and it is now clearly classified as an autoimmune disease associated with genetic and environmental factors, as well as metabolic, oxidative stress, and cell detachment abnormalities [7]. The goal of this study was to see if NLRP1 variation is associated with the risk of generalized vitiligo in a cohort of patients from the Iraqi population. Thus, the researchers genotyped 10 SNPs spread across the NLRP1 gene region in 50 patients with generalized vitiligo and 2504 matched non-vitiligo controls.

Materials and Method

Sample collection

A blood sample (5ml) was collected from (50) GV patients who were referred to dermatology clinics at various hospitals in Iraq. The genomic study population (50 GV patients) was compared to a control group of DNA sequences from 2504 individuals that made public by the 1000 Genomes Database project (https://www.internationalgenome.org/about) [8]. Individuals from the 1000 Genomes Project declared themselves to be healthy at the time they took part in the project study.

SNPs identification

The data slicer interface tool (https://www.internationalgenome.org/data-slicer/) was used to skim the variants data of the NLRP1 promoter region for a total of 2504 individuals from the 1000 Genomes database for the controls genotype identification. Supplementary S-1 contains the complete list of SNPs, their coordinates, and genotype results. The frequency of occurrence of each SNP allele was plotted and is depicted in Figure 1.

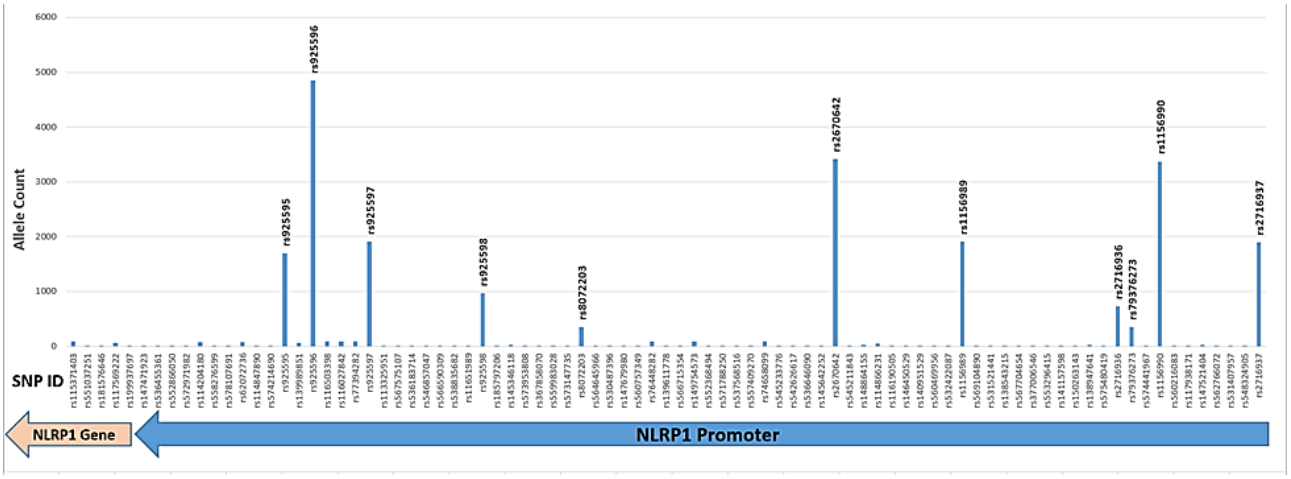

Figure 1: SNPs mapped in the promoter region of the NLRP1 gene, and the allele occurrence of each SNP as reported in the 1000 Genomes Project (1000 genomes)

Whole genomic DNA was extracted from blood sample for NLRP1 patients using a Promega genomic DNA extraction kit. Polymerase Chain Reaction (PCR) was used to amplify the NLRP1 gene promoter region from each sample. The genomic region (2156b) was amplified and the Sanger sequencing method was used to identify each SNP genotype from the GV amplified product.

Primers

Three primers were used (http://bioinfo.ut.ee/primer3-0.4.0/primer3/). Forward primer (ATCCCAGTAAGAGACGACTG), a reverse primer (CTGTGTTCCTCAGATTCTTCC) and internal primer (GAATCTGCAAGATGCCAATG) were designed around region that contains all ten SNPs (rs925595, rs925596, rs925597, rs925598, rs8072203, rs2670642, rs1156989, rs2716936, rs1156990, and rs79376273). The genomic region was amplified at 2156 base pairs (Figure 2).

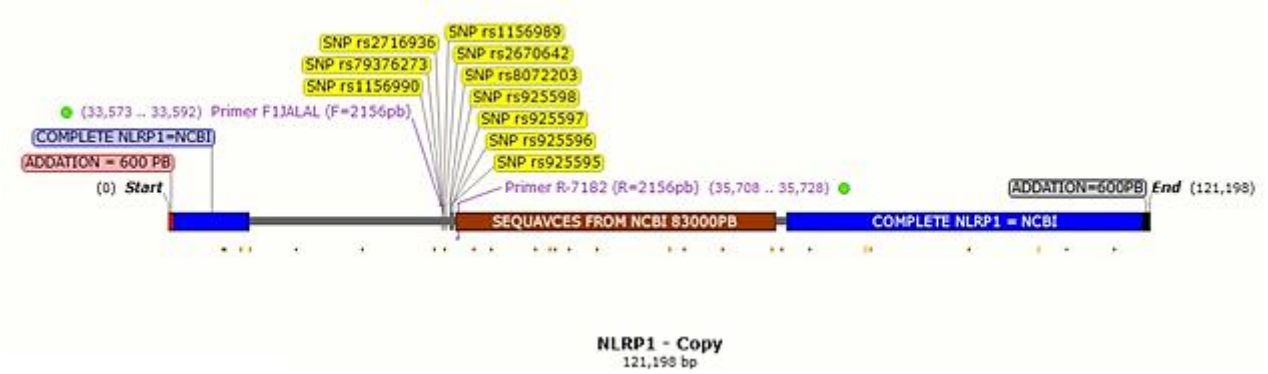

Figure 2: structure of NLRP1 gene (121,198pb)(Snapgene)

Linkage Disequilibrium (LD) mapping

The LDmatrix tool (https://ldlink.nci.nih.gov/?tab=ldmatrix) was used to analyze the likelihood of the six most common SNPs mapped in the NLRP1 promoter being inherited together as a haplotype. Figures display the generated graphical LD heat-map [3, 4].

The used software rSNPBase as a database for curated regulatory SNPs

Statistical analysis

The GV - (allele, genotype, and haplotype) association were estimated using Fisher's exact test described by [9]. The R statistical package (https://www.r-project.org/) was used to calculate odds ratio and confidence intervals for each selected variant and their haplotypes combinations (Figure 3).

Results and Discussion

Genetic markers on the NLRP1 gene are thought to play a role in the susceptibility to autoimmune diseases like GV. Many published studies examined the relationship (or lack thereof) between a single nucleotide polymorphism (SNP) on the NLRP1 gene and GV. To validate previously studied SNPs and include a larger pool of SNPs, the promoter region polymorphism of the NLRP1 was investigated in this study for its association with generalized vitiligo, as indicated in Table 2.

The genotype occurrence pattern of ten SNPs was investigated in a group of 50 generalized GV patients and a population of 2504 individuals from the 1000 Genomes Project (Phase 3). The genotype pattern and allele frequency of these ten SNPs located in the promoter region of the NLRP1 gene are demonstrated in Table 2.

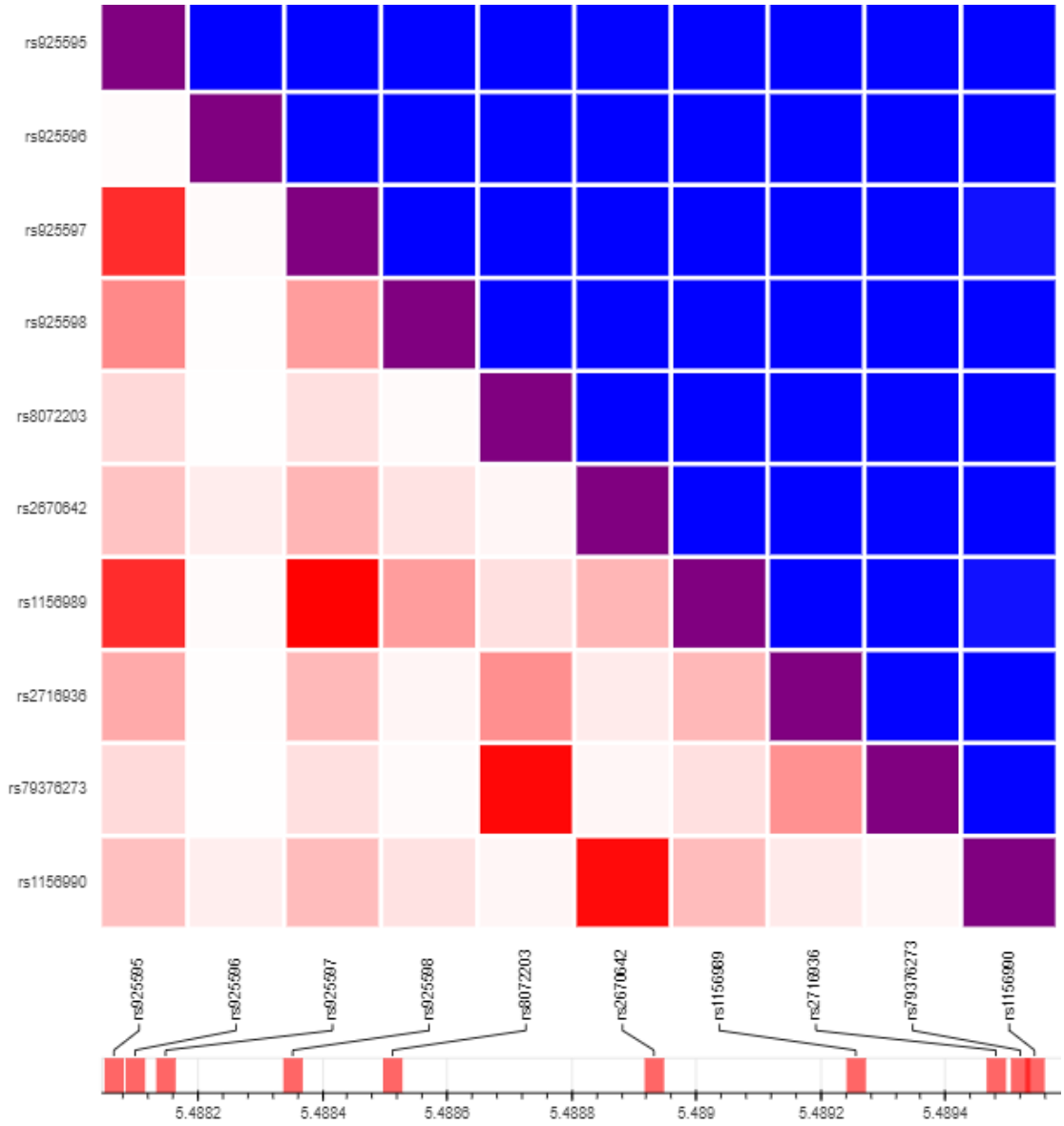

Figure 3: Heatmap matrix of pairwise linkage disequilibrium of 10 polymorphisms in the NLRP1 gene https://ldlink.nci.nih.gov/?tab=ldmatrix

Table1: rSNP Base a database for curated regulatory SNPs

SNP_ID	rSNP	LD-proxy of rSNP(r^2>0.8)	Proximal regulation	Distal regulation	miRNA regulation	RNA binding protein mediated regulation	eQTL
rs1156989	yes	yes	Yes	No	no	No	No
rs1156990	yes	yes	Yes	No	no	No	No
rs2670642	yes	yes	Yes	No	no	No	No
rs2716936	yes	yes	Yes	No	no	No	No
rs79376273	yes	no	Yes	No	no	No	No
rs8072203	yes	yes	Yes	No	no	No	yes
rs925595	yes	yes	Yes	No	no	No	No
rs925596	yes	no	Yes	No	no	No	yes
rs925597	yes	yes	Yes	No	no	No	No
rs925598	yes	yes	Yes	No	no	No	No

Table 2: Genotype and allele distribution of ten polymorphisms in GV patients and 1000 Genomes

SNP	Genotype	GV	1K Genome	Odds Ratio	P- Value
rs1156989	TT	8 (17.3 %)	986 (39.3 %)	(reference)	
T/C	TC	26 (56.5 %)	1125 (44.9 %)	2.85 (1.28 -6.32)	0.0084
	CC	12 (26 %)	393 (15.6 %)	3.76 (1.53-9.28)	0.0045
	T	42 (45.6 %)	3097 (61.8 %)	(reference)	
	C	50 (54.3 %)	1911 (38.1 %)	0.51 (0.33-0.8)	0.0022
rs2716936	CC	35 (76%)	1851 (73.9 %)	(reference)	
C /A,T	CT	9 (19.5%)	576 (23 %)	0.83 (0.39-1.73)	0.72
	TT	2 (4.3 %)	77 (3 %)	1.37 (0.32-5.82)	0.65
	C	79 (85.8 %)	4278 (85. 4 %)	(reference)	
	T	13 (14.1 %)	730 (14.5 %)	1.03 (0.56-2.04)	1
rs79376273	GG	42 (93.35)	2184 (87.2 %)	(reference)	
G /T	GT	2 (4.4 %)	291 (11.6 %)	0.36 (0.09-1.48)	0.229
	TT	1 (2.2 %)	29 (1.15 %)	1.79 (0.24-13.47)	0.44
	G	86 (95.5 %)	4659 (93 %)	(reference)	
	T	4 (2.2 %)	349 (6.9 %)	1.610341 (0.60-6.0)	0.5263
rs1156990	GG	7 (15.5 %)	323 (12.9 %)	(reference)	
G/A,C,T	GA	14 (31.1 %)	989 (39.4 %)	0.65(0.26-1.63)	0.44
	AA	24 (53.3 %)	1192 (47.6 %)	0.93(0.40_ 2.18)	0.82
	G	28 (31.1 %)	1635 (32.6 %)	(reference)	
	A	62 (68.8 %)	3373 (67.3 %)	0.93169 (0.57-1.48)	0.821
rs8072203	CC	41 (91.1 %)	2183 (87.1%)	(reference)	
C/T	CT	1 (2.2%)	290 (11.5 %)	0.18 (0.03-1.34)	0.082
	TT	3 (6.6%)	31 (1.2 %)	5.15 (1.51-17.53)	0.027
	C	83 (92.2%)	4656 (92.9 %)	(reference)	
	T	7 (7.7%)	352 (7.02 %)	0.8964468 (0.41-2.31)	0.6799
rs2670642	CC	2 (4.5%)	304 (12.1%)	(reference)	
C/T	CT	16 (36.3 %)	985 (39.3 %)	2.47 (0.58-10.80)	0.27
	TT	26 (59 %)	1215 (48.5 %)	3.25 (0.77-13.78)	0.09
	C	20 (22.7 %)	1593 (31.8 %)	(reference)	
	T	68 (77.2 %)	3415 (68.1 %)	0.6305679 (0.36-1.05)	0.08227
rs925595	GG	8 (17.7 %)	1131 (45.1 %)	(reference)	
G/C	GC	10 (22.2 %)	1050 (41.9 %)	1.35 (0.53-3.42)	0.63
	CC	27 (60 %)	323 (12.8 %)	11.82 (5.32-26.26)	1.64E-11
	G	26 (28.8 %)	3312 (66.1 %)	(reference)	
	C	64 (71 %)	1696 (33.8%)	0.20(0.12-0.33)	1.402e-12
rs925596	GG	2 (4.5 %)	10 (0.3 %)	(reference)	
G/A,C	GA	2 (4.5 %)	140 (5.5 %)	0.07 (0.01-0.58)	0.03
	AA	40 (90.9%)	2354 (94 %)	0.08 (0.02-0.40)	0.01798
	G	6 (6.8 %), 88	160 (3.1 %)	(reference)	
	A\c	82 (93 %)	4848 (96.8 %)	13.75158 (8.91-20.94)	2.20E-16
rs925597	CC	11 (25 %)	986 (39.3 %)	(reference)	
C/G,T	CT	15 (34 %)	1123 (44.8 %)	1.20 (0.55-2.62)	0.69
	TT	18 (40.9 %)	395 (15.7 %)	4.08 (1.91-8.73)	0.00025
	C	37 (42 %)	3095 (61.8 %)	(reference)	
	T	51 (57.9 %)	1913 (38.1 %)	0.4484893 (0.28-0.70)	0.000231
rs925598	CC	14 (31.8 %)	1668 (67.8 %)	(reference)	
C/T	CT	8 (18 %)	647 (25.8 %)	1.47 (0.62-3.53)	0.47
	TT	22 (50 %)	159 (6.3 5)	16.49 (8.27-32.85)	1.79E-14
	C	36 (40.9 %)	4043 (80.7 %)	(reference)	
	T	52 (59.0 %)	965 (19.2 %)	0.1653244 (0.10-0.25)	4.75E-16

Wang *et al*. (9) proposed that, in addition to CD8 + T cell-mediated killing, the activation of the NLRP1 inflammasome, which leads to increase IL-1 synthesis and release, could be a cause of melanocyte loss at the edges of GV lesions. Capase-1 activation via the inflammasome pathway further causes pyroptosis and inflammatory cell death. Exogenous and endogenous stimulation of

the NLRP1 inflammasome causes acute lung injury in mice, increasing caspase-1 activity towards its downstream substrates and mediating the onset of pyroptosis. One can speculate that NLRP1 inflammasome-mediated apoptosis via caspase-1 is another mechanism for melanocyte destruction, which will be an interesting future research direction [10].

NALP1 variants have recently been linked to GV in Caucasian patients from the United States, the United Kingdom, and Romania [11]. The Middle East has a genetically distinct population. To the best of our knowledge, no comprehensive genetic studies on GV patients from the Middle East have been conducted, and none have looked into the role of NALP1 as a risk factor for GV [12].

The table shows the results of the association between the allele and genotype frequency of the ten selected SNPs and the GV [2]. Five SNP allele frequencies (rs1156989, rs925595, rs925596, rs925597, and rs925598) were significantly (p 0.05) associated with the occurrence of GV disease (0.0022, 1.402e-12, 2.20E-16, 0.000231, and 4.75E-16, respectively). Regular SNPs, which are not only typically found in 5′-upstream regions, but can also be found in transcribed regions and 3′-downstream regions, have an effect on transcription rates [13].

The significant association of the C allele (rs1156989 T/C) with the occurrence of GV is also reflected in the genotypes that carry that allele. The heterozygous TC genotype of rs1156989 is linked to the occurrence of GV, with the odds of having TC genotype in people with GV being 1.85 times higher than in people from the 1000 genomes project (Healthy). The homozygous alternative allele genotype CC of rs1156989 has an even stronger association than the heterozygous genotype; the association of having CC genotype is 2.76 folds stronger in people with GV than in people from the 1000 genomes project.

The rs925596 SNP follows a similar pattern, with the mutant allele a being significantly linked to the GV occurrence. The A allele is dominant (the allele is associated with the disease even if it is polymorphic), as is the C allele of rs1156989, but having homozygous AA or heterozygous GA in rs925596 is associated with a lower risk of GV occurrence. The likelihood of having the GA genotype and AA is slightly less 1 but still significant (p 0.05), indicating an association of these two genotypes with healthy individuals from the 1000 genomes compared with GV patients.

The rs925595, rs925597, and rs925598 loci were found to be recessively linked to GV. The mutant allele of each of the aforementioned variants was associated with a higher risk of GV only when found to be homozygous (P 0.05). The CC genotype of rs925595, the TT genotype of rs925597, and the TT genotype of rs925598 are all linked to an increased risk of developing GV (odds ratio = 11.82, 4.08, and 16.49, respectively). In the United States, the United Kingdom, and Romania, Jin *et al*. conducted extensive studies on NLRP1 variations in GV patients. Specific single nucleotide polymorphisms (SNPs) of NLRP1 have been found to increase susceptibility to GV, including rs6502867/A, rs961826/A, rs925598/A, rs878329/G, rs3926687/T, rs7223628/G, rs12150220/A, and rs2670660/C. Three loci, rs6502867, rs2670660, and rs8182352, were found to be associated with vitiligo in Romanian patients. These were some of the same SNPs, involving the same high-risk alleles linked to disease in families from the United States and the United Kingdom [11]. SNP rs8074853, located 6.8 kb upstream from rs6502867, was found to be marginally associated with disease in our previous study [14], and it was found to be marginally associated in this study, as well. SNP rs16954840, which is only 3.2 kb upstream, showed no association with disease in either of our previous studies [14].

The adapter protein ASC, caspase 1, and caspase 5 are recruited by NALP1 to form the NALP1 inflammasome, which activates the proinflammatory cytokine interleukin-1 [15]. Serum interleukin-1 levels are elevated in patients with generalized vitiligo [16], implying that this pathway is involved in disease pathogenesis. NALP1 appears to be involved in cellular apoptosis as well, with overexpression stimulating caspase-mediated apoptosis in a variety of cell types [17].

Analyses of Linkage Disequilibrium (LD) and Haplotypes of NLRP1 Promoter Polymorphisms

Linkage disequilibrium (LD) variants are likely to be inherited on the same piece of DNA. Using the 1000 Genomes database, the LD tool was used to generate a correlation heatmap figure in order to identify SNPs with high linkage disequilibrium (Figure 3). The study of ten SNPs with high frequency in the NLRP1 promoter region revealed the highest correlation among three SNPs (rs925595, rs925597, and rs1156989). The solid red color of the crossed SNPs represents the high correlation between these three SNPs. The rest of the variants, which are distinguished by their faded red coloration, have a lower correlation. SNPs with low to moderate correlation were excluded from further investigation. The downstream haplotype analysis included only the three most popular SNPs (rs925595, rs925597, and rs1156989) displayed in Figure 4. Three loci, rs6502867, rs2670660, and rs8182352, were found to be associated with GV in Romanian patients. These were some of the same SNPs, involving the same high-risk alleles linked to disease in families from the United States and the United Kingdom [11]. SNP rs8074853, located 6.8 kb upstream of rs6502867, was found to be marginally associated with disease in our previous study [14], and it was found to be marginally associated in this study, as well. SNP rs16954840, which is only 3.2 kb upstream, showed no association with disease in either of our previous studies [14]. The count and frequency analysis of the haplotypes constructed of the rs925595, rs925597, and rs1156989 SNPs revealed a total of 10 haplotypes listed in Table 3. The common haplotypes inferred from the patients and the 1000 genomes database were four in total (color-coded grey) in Table 3. Two other haplotypes were inferred exclusively from the vitiligo patients (color-coded dark grey). They were not presented in any of 1000 genomes individuals. In contrast, three haplotypes were found solely in individuals from 1000 genomes (color-coded white) while not in any vitiligo patient's samples.

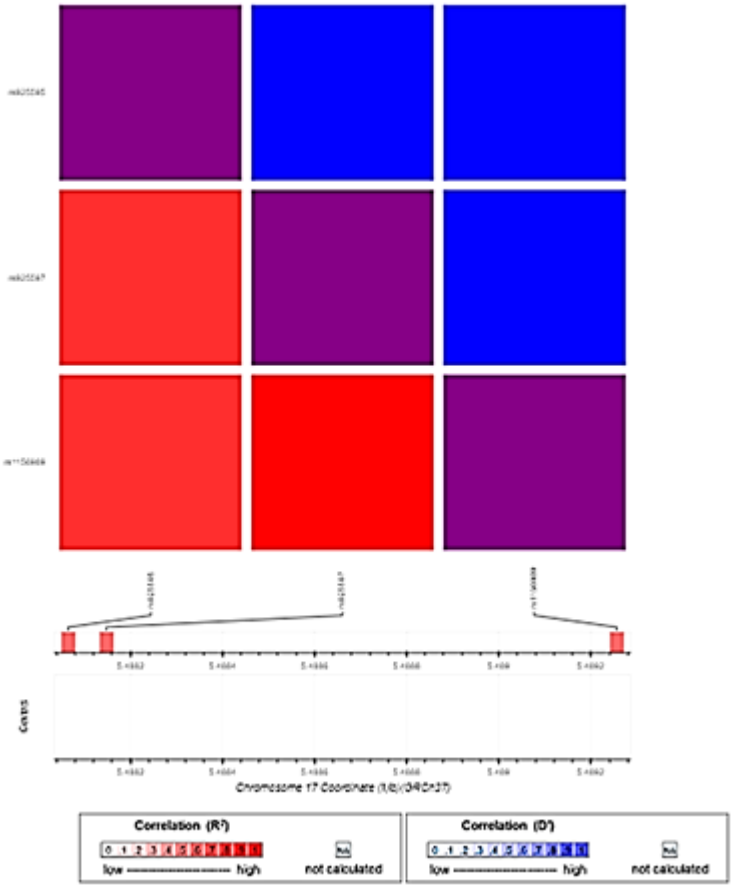

Figure 4: Heatmap matrix of pairwise linkage disequilibrium of 3 polymorphisms in the NLRP1 gene https://ldlink.nci.nih.gov/?tab=ldmatrix

The results highlight important findings, as these patient-specific haplotypes could be used as a biomarker to predict vitiligo predisposition in humans. The patient-specific haplotypes (color coded dark grey) had an odd ratio of infinity and infinity statistical significance as they were present only in patients and non in the control group (Table 3). Out of the four of the 10 inferred haplotypes that were common and found in both patients and 1K genomes individuals (color-coded grey in Table 3), H1 haplotype is one of the common haplotypes and was used as a reference in the statistical analysis performed. H2 and H4 haplotypes are another common haplotype among the patients and the control group, yet no statistically significant difference was seen in the occurrence of this haplotype between the two groups. Two more common haplotypes (H3 and H8) were common among vitiligo patients and the control group and they were all significantly associated with a high risk of vitiligo ($p \leq 0.05$) with the highest OR to H8 [OR (CI) = 1,163(123.4-10,967)]. Three out of the 10 haplotypes were only present in the 1K genome individuals (color-coded white) Table 3. H5 haplotype had the highest frequency (2.08%) in the 1K genome individuals, followed by H6 (0.80%), and lastly, H7 (0.04%). However, none of the 1K genome's specific haplotypes were statistically significant, as the reference haplotype reflects high observed frequency in the 1K genomes (39.82%) vs. frequency of only (20.7) in the patient's individuals.

Table 3: Haplotypes analysis consisted of (-334, -226, and -25 SNPs) reveals association with GV

Haplotypes	rs925595 G/C	rs925597 C/G	rs1156989 T/C	No. of haplotypes		Frequency (%)			
				In Patients	In 1K genomes	In patients	In 1K genomes	p-value	OD (CI)
H1	GC	CT	TC	6	997	20.7	39.82	Reference	Reference
H2	GG	CC	TT	6	986	20.7	39.38	1	1.01(0.33-3.15)
H3	CC	TT	CC	8	321	27.59	12.82	0.009	4.14(1.43-12.02)
H4	GG	CT	TC	1	125	3.45	4.99	0.56	1.33(0.16-11.13)
H5	GC	TT	CC	0	52	0.00	2.08	1	0.00(0,00-?)
H6	GG	TT	CC	0	20	0.00	0.80	1	16.6(1.66-166.74)
H7	GC	TT	TC	0	1	0.00	0.04	1	332.33(16.6-638.7)
H8	CC	CT	TC	7	1	24.14	0.04	6.50943E-14	1,163 (123.4-10,967)
H9	CC	TT	TC	1	0	3.45	0.00	0.0069	Infinity (? - infinity)
H10	GG	CC	TC	1	0	3.45	0.00	0.0069	Infinity (? - infinity)

Dwivedi *et al*. [18] discovered that NLRP1 rs2670660 and rs6502867 polymorphisms may be genetic risk factors for GV susceptibility and progression in a Gujarat population. The up-regulation of NLRP1 mRNA in patients with susceptible genotypes supports NLRP1's critical role in GV. Three of the 15 haplotypes were found only in the 1K genome individuals (color-coded light grey), as indicated in Table (3). The H2 haplotype was the most common (39.38 percent) in the 1K genome individuals, followed by H3 (12.82) and finally, H5 (2.08 percent). However, none of the 1K genome's specific haplotypes were statistically significant, as the reference haplotype has a high observed frequency in the 1K genomes (39.82 percent), but only a 7.32 percent frequency was found in the patient's individuals.

Conclusions

The investigation on the 10 SNPs with high frequency in the NLRP1 promoter region revealed the highest correlation among three SNPs (rs925595, rs925597 and rs1156989). The findings suggest that NLRP1 polymorphisms (*rs1156989, rs925595, and rs925597*) are linked to the development of generalized vitiligo in the Iraqi patient population when compared to individuals from the 1000 genomes project.And can submit haplotype H8 as biomarker to predicated in autoimmune diseases (vitiligo).

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Authors' contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

Conflict of Interest

There are no conflicts of interest in this study.

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References

[1]. Desai M.K., Brinton R.D., Autoimmune Disease in Women: Endocrine Transition and Risk Across the Lifespan, *Frontiers in endocrinology*, 2019, **10**:265 [Crossref], [Google Scholar], [Publisher]
[2]. Bergqvist C., Ezzedine K., Vitiligo: a review, *Dermatology*, 2020, **236**:571 [Crossref], [Google Scholar], [Publisher]
[3]. de Baat C., Phoa K.H., Zweers P.G.M.A., Bolling M.C., Rozema F.R., Vissink A., Serie: Medicamenten en mondzorg. Hyperpigmentatie van de orale slijmvliezen door afamelanotide, *Nederlands tijdschrift voor tandheelkunde*, 2020, **127**:237 [Crossref], [Google Scholar], [Publisher]
[4]. Yu R., Broady R., Huang Y., Wang Y., Yu J., Gao M., Levings M., Wei S., Zhang S., Xu A., Su M., Dutz J., Zhang X., Zhou Y., Transcriptome analysis reveals markers of aberrantly activated innate immunity in vitiligo lesional and non-lesional skin, *PLoS One*, 2012, **7**:e51040 [Crossref], [Google Scholar], [Publisher]
[5]. Rahman R., Hasija Y., Exploring vitiligo susceptibility and management: a brief review, *Biomedical Dermatology,* 2018, **2**:1 [Crossref], [Google Scholar], [Publisher]
[6]. Das S.K., Majumder P.P., Chakrabotry R., Majumdar T.K., Haldar B., Rao D.C., Studies on vitiligo I. Epidemiological profile in Calcutta, India. *Genetic epidemiology*, 1985, **2**:71 [Crossref], [Google Scholar], [Publisher]
[7]. Chen J., Li S., Li C., Mechanisms of melanocyte death in vitiligo, *Medicinal Research Reviews*, 2021, **41**:1138 [Crossref], [Google Scholar], [Publisher]
[8]. The 1000 Genomes Project Consortium, Aglobal reference for human genetic variation, *Nature*, 2015, **526**:68 [Crossref], [Google Scholar], [Publisher]
[9]. Wang X.X., Wang Q.Q., Wu J.Q., Jiang M., Chen L., Zhang C.F., Xiang L.H., Increased expression of CXCR3 and its ligands in patients with vitiligo and CXCL10 as a potential clinical marker for vitiligo, *British Journal of Dermatology*, 2016, **174**:1318 [Crossref], [Google Scholar], [Publisher]
[10]. Chen R.H., Zhang R.Z., Nucleotide oligomerization domain-like receptor protein 1 inflammasome and vitiligo: progress in understanding the relationship, *International Journal of Dermatology and Venereology*, 2019, **2**:24 [Crossref], [Google Scholar], [Publisher]
[11]. Jin Y., Birlea S.A., Fain P.R., Spritz R.A., Genetic variations in NALP1 are associated with generalized vitiligo in a Romanian population, *Journal of Investigative Dermatology*, 2007, **127**:2558 [Crossref], [Google Scholar], [Publisher]
[12]. Alkhateeb A., Qarqaz F., Genetic association of NALP1 with generalized vitiligo in Jordanian Arabs, *Archives of dermatological research*, 2010, **302**:631 [Crossref], [Google Scholar], [Publisher]
[13]. Degtyareva A.O., Antontseva E.V., Merkulova T.I., Regulatory SNPs: altered transcription factor

binding sites implicated in complex traits and diseases, *International journal of molecular sciences*, 2021, **22**:6454 [Crossref], [Google Scholar], [Publisher]

[14]. Jin Y., Mailloux C.M., Gowan K., Riccardi S.L., LaBerge G., Bennett D.C., Fain P.R., Spritz R.A., NALP1 in vitiligo-associated multiple autoimmune disease, *New England Journal of Medicine*, 2007, **356**:1216 [Crossref], [Google Scholar], [Publisher]

[15]. Zheng D., Liwinski T., Elinav E., Inflammasome activation and regulation: toward a better understanding of complex mechanisms, *Cell discovery,* 2020, **6**:1 [Crossref], [Google Scholar], [Publisher]

[16]. Tomaszewska K., Kozłowska M., Kaszuba A., Lesiak A., Narbutt J., Zalewska-Janowska A., Increased serum levels of IFN-γ, IL-1β, and IL-6 in patients with alopecia areata and nonsegmental vitiligo. *Oxidative Medicine and Cellular Longevity*, 2020, **2020** [Crossref], [Google Scholar], [Publisher]

[17]. Liu F., Lo C.F., Ning X., Kajkowski E.M., Jin M., Chiriac C., Gonzales C., Naureckiene S., Lock Y.W., Pong K., Zaleska M.M., Jacobsen J.S., Silverman S., Ozenberger B.A., Expression of NALP1 in cerebellar granule neurons stimulates apoptosis, *Cellular Signalling*, 2004, **16**:1013 [Crossref], [Google Scholar], [Publisher]

[18]. Dwivedi M., Laddha N.C., Mansuri M.S., Marfatia Y.S., Begum R., Association of NLRP1 genetic variants and mRNA overexpression with generalized vitiligo and disease activity in a Gujarat population, *British Journal of Dermatology*, 2013, **169**:1114 [Crossref], [Google Scholar], [Publisher]

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