

Serum Levels and Genetic Polymorphisms of Matrix Metalloproteinase-9 (MMP-9) in Patients with Scabies

Noora D. Abd^{1*}, Nagham Y. Albayati¹, Ali H. Abbas²

¹Department of Biology, College of Education for Pure Sciences, University of Diyala

²Topical-Biological Research Unit, College of Sciences, University of Baghdad

ABSTRACT

Background: Scabies is a contagious parasitic skin disease caused by *Sarcoptes scabiei* var. *hominis*, leading to severe itching, dermatitis, and skin lesions. The infection triggers host immune responses, activating T and B lymphocytes and inducing both cellular and humoral immunity, along with an allergic reaction. Matrix metalloproteinase-9 (MMP-9) is a zinc-dependent enzyme involved in extracellular matrix (ECM) remodeling and tissue degradation, playing a crucial role in inflammatory and immune-mediated skin disorders. This study investigates serum MMP-9 levels and genetic polymorphisms in patients with scabies to assess their potential role in disease susceptibility. **Methods:** A case-control study was conducted at Baquba Teaching Hospital, Dermatology Unit, Diyala Governorate, from December 4, 2022, to June 10, 2023. A total of 75 patients diagnosed with scabies and 75 age- and sex-matched healthy individuals were enrolled as controls. Serum MMP-9 levels were measured, and allele-specific primer polymerase chain reaction (ASP-PCR) was used to analyze MMP-9 gene polymorphisms at rs17576 and rs760670157. **Results:** MMP-9 levels were significantly elevated in scabies patients compared to the control group ($p < 0.05$). Genetic analysis revealed an increased frequency of the GG and TG genotypes, along with a higher prevalence of the G allele in scabies patients at the rs17576 locus, suggesting an association with disease susceptibility. Conversely, the TT genotype and T allele were less frequent in the scabies group. At the rs760670157 locus, the GA genotype and A allele were more prevalent in scabies patients, whereas the GG and AA genotypes and G allele were found at lower frequencies compared to controls. **Conclusion:** This study suggests that MMP-9 gene polymorphisms may be associated with susceptibility to scabies. The presence of TG and GG genotypes, as well as the G allele at rs17576, and the GA genotype and A allele at rs760670157, appear to be risk factors for scabies development. Further research is needed to explore the functional impact of these polymorphisms on MMP-9 expression and their role in scabies pathogenesis.

Keywords: Scabies, MMP-9, Genotypes, rs17576, rs760670157

INTRODUCTION

Scabies is a skin disease caused by a microscopic ectoparasite *Sarcoptes scabiei* var. *hominis* [1]. The disease causes severe itching all over the body, especially between the fingers, genital area, and breasts in females, around the navel and armpits [2]. The disease affects both sexes and all ages all over the world, and its spread increases in tropical and subtropical regions [3]. According to World Health Organization reports, at least 200-300 million people are infected with the disease annually, however it still among the neglected tropical diseases [4]. The disease spreads in crowded places such as schools, nursing homes, and orphanages, and it also spreads among large families [5]. Scabies remains without symptoms for 4-8 weeks, and during this period the person carrying the disease causes infection to other people, and this is the reason why the disease spreads rapidly [6]. The disease manifests itself in the form of severe itching that increases at night and the appearance of burrows, papules, and nodules. Female mites dig canals into the skin to lay eggs, which, along with waste and saliva, cause the induction of cellular and humoral immunity and allergic reactions [7]. Mites antigens induce local inflammatory and both type I and type IV hypersensitivity reactions causing by infiltration of many inflammation cells keratinocytes, neutrophils, Langerhans cells, and macrophages that modulate the immune reaction and induce cytokines and other immune cell secretes production including mast cells the recruitment of these secretes and cells to infection site especially eosinophils, mast cells, and basophils lead to inflammatory and hypersensitivity reactions [8]. The disease causes an increase in the expression of helper T cells and an increase in the level of some interleukins, such as IL-4, IL-5, IL-13, IL-17, and IgE

antibodies [9]. Matrix metalloproteinase-9 It is a protein that belongs to the family of proteins that bind to minerals, especially zinc, and it has a role in reorganizing peptides that can break down and decompose most extracellular matrix (ECM) [10]. MMP-9 has a role in the processes of apoptosis, the distribution of growth factors, and the integration of cellular signals, as well as its role in inflammatory injuries and wound healing [11]. MMP-9 is mainly produced by macrophages, neutrophils, endothelial cells, mast cells, and fibroblasts, and the change in it leads to chronic diseases, cancer, and neurological diseases [12, 13]. The aim of the present research was to determine the serum level and genetic variations of MMP-9 rs17576 and rs760670157 in scabies patients in comparison to a group of healthy individuals.

MATERIALS AND METHODS

The current study included 75 patients infected with scabies (41 males and 34 females) from the patients attending Baqubah Teaching Hospital / Consultation Clinic / Dermatology Unit in Diyala Governorate, and 75 healthy people (45 males and 30 females). After ensuring that they were free from infectious and communicable diseases and conducting a complete blood count examination, they were considered as a control group. The collection of samples was done during the period between December 2022 to June 2023, five ml of venous blood was drawn from both study groups, and 2 ml were placed in an EDTA tube to conduct a genomic experiment of MMP-9 gene polymorphisms rs17576 and rs760670157.

Three ml were placed in a silicone gel tube to extract the serum and measure the MMP-9 concentration level in both study groups using human MMP-9 ELISA kit. Also, deoxyribonucleic acid (DNA) was extracted by using a kit and according to the instructions of the manufacturer INTRON Company (Korea). The concentration and

purity were measured using Nanodrop. The primers were designed by NCBI-Primer Blast Online Website, and they were prepared according to the instructions of Alpha-DNA Company (Canada). Tables 1 and 2 showed the sequences and PCR amplicon product size of MMP-9 rs17576 and rs760670157.

Table 1: MMP-9 SNPs of rs17576 Primers Information

MMP-9 SNP Rs17576	Sequence (5' > 3')	Product Length
Common Forward Primer	CACTAGTGCTGTGTGGCCTG	213 bp
Reverse Primer #1	CCATCAGCATTGCCGTCTT	
Reverse Primer #2	CCATCAGCATTGCCGTCTG	

Table 2: MMP-9 SNPs of rs760670157 Primers Information

MMP-9 SNP Rs760670157	Sequence (5' > 3')	Product Length
Forward Primer #1	TGACTTCCAGTCCCTCCCC	182 bp
Forward Primer #2	TAACTTCCAGTCCCTCCCC	
Common Reverse Primer	AGGGTCCTTTCAGCCCTAAC	

The researchers used allele-specific primer-polymerase chain reaction (ASCR-PCR) to identify single nucleotide polymorphisms (SNPs) in the MMP-9 gene at positions rs17576 and rs760670157. The method for testing MMP-9 rs17576 involved using 2 Eppendorf tubes (0.2 ml) for each sample. In the first tube, 12.5 µl of master mix (from Trans gene-biotech company, Korea), 1 µl of common forward primer, and 1 µl of reverse primer #1 were added. In the second tube, 1 µl of common forward primer and 1 µl of reverse primer #2 were added. 2 µl of DNA was added to each tube, and the volume was then brought to 25 µl with free nucleases water. The procedure for MMP-9 rs760670157 was demonstrated using 2 Eppendorf tubes. The Thermo cycler protocol for both MMP-9 SNPs consisted of three steps: the first involved one cycle of primary initiation at 95 degrees Celsius for 10 minutes, the second step included initiation at 95 degrees Celsius for 35 seconds, followed by extension at 61 degrees Celsius for 35 seconds, and

elongation at 72 degrees Celsius for 35 seconds. This step was repeated 35 times. The final step was one cycle at 72 C° for 10 minutes. The PCR amplicons were visualized by electrophoresis on 1.5 % agarose gel stained with Red Safe stain®, the bands were visualized by transilluminator UV at 350 nm.

Results

The results of the current study found the concentration rates of MMP-9 in the sera of the study groups, indicated increased levels among the infected compared to the control group (26.38 ± 1.72 vs. 19.49 ± 1.62 pg/ml). While the levels were not significantly increased in both infected sexes compared to the sexes of the controls (24.47 ± 2.25 vs. 18.24 ± 2.0 pg/ml for males, 28.68 ± 2.65 vs. 21.47 ± 2.75 pg/ml for females) according to results represented in Table3.

Table3: The Serum Level of MMP-9 between the Studied Groups

Sexes	MMP-9 level Mean $\pm$ SD (pg/ml)		Probability
	Patients Group(N=75)	Control Group(N=75)	
Males	24.47 ± 2.25	2.0 ± 18.24	0.248
Females	28.68 ± 2.65	2.75 ± 21.47	0.170
Total	26.38 ± 1.72	1.62 ± 19.49	0.004
Probability	0.125	0.352	

The DNA extraction experiment, the purity of the extracted DNA was 1.8 – 2, while its concentration was between 50-100/ml, which was calculated by nanodrop. The findings from the genetic variation analysis of MMP-9 SNPs rs17576 showed the existence of two alleles T and G which resulted in three genotypes TT, TG, and GG. The genotypes were analyzed using allele-specific primers – polymerase

chain reaction (ASP-PCR) [14-16], indicating that TT homozygote genotype produced a single band with reverse primer #1, GG homozygote genotype produced a single band with reverse primer #2, and TG heterozygote genotype showed two bands on agarose gel with reverse primer #1 in the first well and reverse primer #2 in the second well, as illustrated in Figure 1.

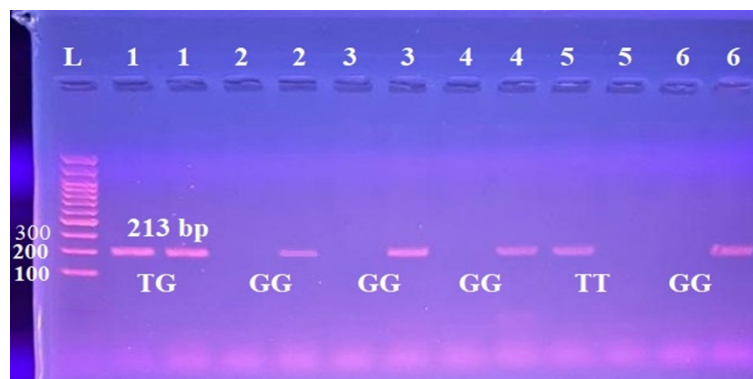


Figure 1: Agarose Gel Electrophoresis of MMP-9 SNPs rs17576 PCR Product on 1.5% Agarose Gel Stained with Red Safe Stain® (Transgenbiotech Company, Korea) for 40 Minutes at 100 Voltages. L: Universal DNA Ladder (Transgenbiotech Company, Korea), 1–6: Electrophoresed Samples' Numbers, the Single Bands Referred to the Wild TT Genotypes and the Mutated GG Genotype, while the Two Bands Referred to the TG Genotype.

The analysis of MMP-9 SNP rs17576's genotyping and allele frequencies revealed that the genotypes present in the scabies group did not align with the Hardy – Weinberg equilibrium, with a P-value of 0.0193. Conversely, the healthy control group showed no variation, rendering the calculation of the Hardy – Weinberg equilibrium's probability unnecessary (Table 4). The study found that the genotype and allele frequencies for TG and G were notably higher in the scabies group when compared to the control group (14.67% vs. 0.0%, OR: 26.92, pc: 3.1×10^{-4} and 11.0% vs. 0.0%, OR: 39.46, pc: 4.5×10^{-6} ,

respectively) (Table 5). Regarding the GG genotype, there was a non-significant increase in its percentage among the scabies group when compared to the control group (4.0% vs. 0.0%, OR: 7.29, pc: 0.120). The elevated OR values for the TG, GG genotype, and G allele could suggest a relative risk for scabies (Table 5). On the other hand, the percentage of TT genotype and T allele was significantly lower in the scabies group when compared to the control group (81.33% vs. 100.0%, OR: 0.01, pc: 2.8×10^{-5} and 89.0% vs. 100.0%, OR: 0.03, pc: 4.5×10^{-6} , respectively) (Table 5).

Table 4: The MMP-9 SNPs rs17576 Genotyping Frequencies and Hardy Weinberg Compatibility in the Patients' Group Compared to Controls

Genotyping Frequencies Of MMP-9 Rs17576	Patients Group (N=75)		Control Group (N=75)	
	Observed	Expected	Observed	Expected
TT	61(81.33)	58.96(78.62)	75(100.0)	75(100.0)
TG	11(14.67)	15.07(20.10)	0(0.0)	0(0.0)
GG	3(4.0)	0.96(1.28)	0(0.0)	0(0.0)
Total	75(100.0)	75(100.0)	75(100.0)	75(100.0)
P-HWE	0.0193		-	

Table 5: The MMP-9 SNPs rs17576 Genotypes and Alleles Frequencies in the Patients' Group Compared to Controls

Genotyping and Alleles Frequencies Of MMP-9 Rs17576	Patients Group (N=75)	Control Group (N=75)	OR (95% CI)	P-Value
T	133(89.0)	150(100.0)	0.03(0.002-0.43)	9.4×10^{-6}
G	17(11.0)	0(0.0)	39.46(2.37-656.30)	9.4×10^{-6}
TT	61(81.33)	75(100.0)	0.01(0.001-0.24)	6.3×10^{-5}
TG	11(14.67)	0(0.0)	26.92(1.59-457.15)	6.6×10^{-4}
GG	3(4.0)	0(0.0)	7.29(0.38-140.81)	0.245
Total	75(100.0)	75(100.0)		0.120

OR: Odd Ratio, 95% CI: 95% Confidence Intervals, P-Value: Fisher's Exact Probability Value, Pc-Value: Bonferroni Corrected Probability Value

In addition, the present results showed a significantly increased level of MMP-9 in the scabies group having the TT genotype compared to the controls (26.91 ± 14.38 vs. 19.49 ± 14.06 pg/ml) (Table 6).

Such, results showed a non-significant increased level of MMP-9 in the individuals with the TG genotype compared to the TT and GG genotypes in the scabies group (Table 6).

Table 6: MMP-9 Serum Levels According to the MMP-9 SNPs rs17576 of the Studied Groups

Genotyping Frequencies Of MMP-9 Rs17576	MMP-9 Serum Level Mean $\pm$ SD (Pg/Ml)		Probability
	Patients Group	Control Group	
TT	26.91 ± 14.38^A	19.49 ± 14.06	0.003
TG	27.04 ± 18.80^A	-	-
GG	13.07 ± 3.15^A	-	-

Duncan Test: The Similar Letters Referred to Non-Significant Differences ($P > 0.05$) Between the Genotyping of the Same Group

Concerning the MMP-9 SNPs rs760670157, two different versions of the gene (G and A) were identified, leading to three possible genetic combinations (GG, GA, AA), identified using specific DNA primers in a technique called allele-specific polymerase chain reaction (ASP-PCR) [14-16]. This analysis revealed that the GG genotype, which is the wild-type homozygote, was represented by a single band in the first well when the DNA was run through an agarose gel using the forward #1

primer. The GA genotype, which is a heterozygote, was shown to have two bands in the first well with the forward #1 primer and another well with the forward #2 primer.

Furthermore, the AA genotype, which is a mutated homozygote, was identified by a single band in the second well with the forward #2 primer during the gel electrophoresis process, as illustrated in Figure 2.

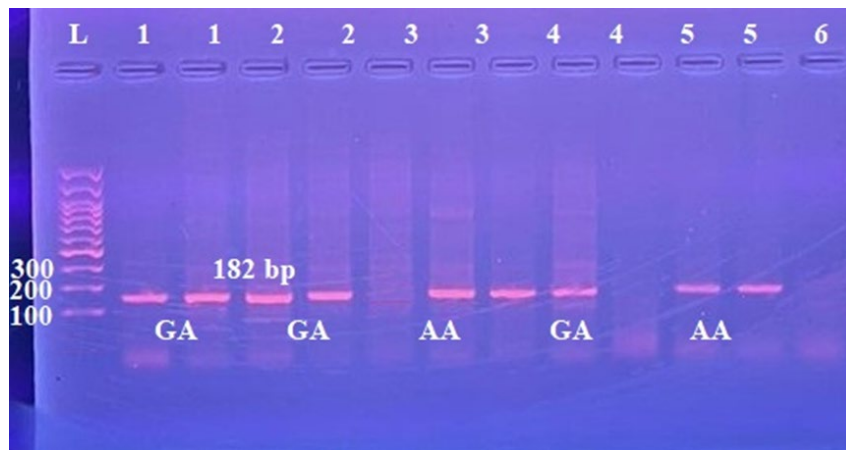


Figure 2: Agarose Gel Electrophoresis of MMP-9 SNPs Rs760670157 PCR Product on 1.5% Agarose Gel Stained with Red Safe Stain® (Transgenbiotech Company, Korea) for 40 Minutes at 100 Voltages. L: Universal DNA Ladder (Transgenbiotech Company, Korea), 1–6: Electrophoresed Samples' Numbers, the Single Bands Referred to the GG Genotype, while the Two Bands Referred to the GA Genotype.

The genotyping and allele frequencies of MMP-9 SNP rs760670157 showed that the genotypes of the scabies group were incompatible with the Hardy–Weinberg equilibrium, while the healthy control group was compatible (P-value: 16.0×10^{-11} , 0.0846, respectively) (Table7).

The genotype GA percentage was significantly increased in the scabies group compared to the control group (86.7% vs. 58.7%, OR: 4.58, pc: 1.0×10^{-4}), while the A allele showed a non-significantly

increased percentage in the scabies group compared to the control group (47.0% vs. 43.0%, OR: 1.21, pc: 0.420). In contrast, the GG and AA genotypes showed a significantly decreased percentage in the scabies group compared to the control group (9.3% vs. 28.0%, OR: 0.26, pc: 3.3×10^{-3} and 4.0% vs. 13.3%, OR: 0.27, pc: 0.046, respectively) (Table 8), while the G allele showed a non-significantly decreased percentage in the scabies group compared to the controls (53.0% vs. 57.0%, OR:0.83, pc: 0.420) (Table8).

Table 7: The MMP-9 SNPs rs760670157 Genotyping Frequencies and Hardy Weinberg Compatibility in the Patients' Group Compared to Controls.

Genotyping Frequencies Of MMP-9 Rs760670157	Patients Group (N=75)		Control Group (N=75)	
	Observed	Expected	Observed	Expected
GG	7(9.3)	20.8(27.7)	21(28.0)	24.7(32.9)
GA	65(86.7)	37.4(49.9)	44(58.7)	36.7(48.9)
AA	3(4.0)	16.8(22.4)	10(13.3)	13.7(18.2)
Total	75(100.0)	75(100.0)	75(100.0)	75(100.0)
P-HWE	16.0x10 ⁻¹¹		0.0846	

P-HWE: probability of Hardy-Weinberg equilibrium

Table 8: The MMP-9 SNPs rs760670157 Genotypes and Alleles Frequencies in the Patients' Group Compared to Controls

Genotyping and Alleles Frequencies Of MMP-9 Rs760670157	Patients Group (N=75)	Control Group (N=75)	OR (95% CI)	P-Value	Pc-Value
G	79(53.0)	86(57.0)	0.83(0.53-1.30)	0.486	0.420
A	71(47.0)	64(43.0)	1.21(0.77-1.90)	0.486	0.420
GG	7(9.3)	21(28.0)	0.26(0.11-0.66)	5.7×10^{-3}	3.3×10^{-3}
GA	65(86.7)	44(58.7)	4.58(2.05-10.23)	2.0×10^{-4}	1.0×10^{-4}
AA	3(4.0)	10(13.3)	0.27(0.07-1.02)	0.078	0.046
Total	75(100.0)	75(100.0)			

OR: Odd Ratio, 95% CI: 95% Confidence Intervals, P-Value: Fisher's Exact Probability Value, Pc-Value: Bonferroni Corrected Probability Value

Also, the results of MMP-9 SNP rs760670157 showed a significantly increased level in the scabies group having the GA and AA genotypes compared to the controls (25.60 ± 15.44 vs. 18.55 ± 13.83 pg/ml and 39.80 ± 16.75 vs. 19.93 ± 16.39 pg/ml, respectively) (Table

9). Such, results showed a non-significant arising in MMP-9 level in the individuals with the AA genotype in comparison with the GG and AG genotypes in the scabies group, and GG genotype compared to the AG and AA genotypes in the control group (Table).

Table 9: MMP-9 Serum Levels According to the MMP-9 SNPs rs760670157 of the Studied Groups

Genotyping Frequencies Of MMP-9 Rs760670157	MMP-9 Serum Level Mean $\pm$ SD (Pg/Ml)		Probability
	Patients Group	Control Group	
GG	27.83 $\pm$ 3.81 ^A	21.25 $\pm$ 13.94 ^A	0.301
GA	25.60 $\pm$ 15.44 ^A	18.55 $\pm$ 13.83 ^A	0.014
AA	39.80 $\pm$ 16.75 ^A	19.93 $\pm$ 16.39 ^A	0.040

Duncan test: The similar letters referred to non-significant differences ($P > 0.05$) between the genotyping of the same group

Discussion

Scabies is one of the parasitic infections caused by the *Sarcoptes scabiei* var *hominis* that affects millions of people over the world per year. The present study was the first study that dealt with MMP-9 among scabies patients. Even the present findings of the MMP-9 serum level increasing in the scabies patients' group were compatible with other previous studies such as Epilepsy [17]. And in Diabetes type 2 [18]. And Coronary artery disease [19]. As for the results of the MMP-9 SNPs rs17576 and rs760670157, they have been studied for the first time in scabies. But when comparing the present findings of MMP-9 SNPs rs17576 and rs760670157 with another previous study conducted by Saravani et al. [20] indicated that this gene is considered a risk

factor for developing type 2 diabetes. Wu et al. [21] also indicated that the gene is linked to cardiovascular diseases. A study conducted by Sarvanan et al. [22] also indicated its association with neurological and psychological diseases and that the variations of Genetics in it are responsible for depression, and this confirms the relationship of the gene concerned with many diseases, including scabies, as shown by the current study.

Conclusion

The study concluded that the mmp-9 related to scabies infection and, that the TG, GG genotypes, and the G allele for MMP-9 gene SNPs rs17576 further to the GA genotype and the A allele for MMP-9 gene SNPs rs760670157 are risk factors for the development of the disease.

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