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Research Article

The Correlation between Caspase-1 Polymorphisms and COVID-19 Severity Score of Recovered Iraqi Patients

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I N F O

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A B S T R A C T

Severe Acute Respiratory Syndrome Corona Virus-2, responsible for the Coronavirus disease 2019 (COVID-19) pandemic, is a single-stranded RNA-enveloped virus encoding 9860 amino acids. Coronavirus particles contain structural and non-structural proteins. The S, E, M, and N genes code for structural proteins, while the Open Frame Reading (ORF) region codes for nonstructural proteins like 3-chymotrypsin-like protease, papain-like protease, and RNA-dependent RNA polymerase. This study aimed to provide local data about SNP rs580253 and rs551684387 Casp1 genotype for Iraqi patients with various infections caused by coronavirus.

Eighty blood samples were collected between November 2020 and February 2021, with the age of patients ranging from 20 to 65 years. The sample comprised 50 patients diagnosed with COVID-19 (23 males and 27 females) from the hospitals in Baghdad, and 30 matched apparently healthy subjects as control (20 males and 10 females). All of them underwent PCR tests. The samples of 50 patients were divided into sub-groups according to the severity (mild, moderate, and severe).

The statistical analysis of rs580253 showed that there was no significant difference between control and patient groups (p-value = 0.63). The comparison between the cases, for mild, moderate and severe cases showed that there was no significant difference between cases. Also, the statistical analysis of SNP rs551684387 Casp showed that there was no significant difference between control and patient groups. The comparing between the mild, moderate, and severe cases showed no significant difference between the severity of cases.

According to our study, we thought that there is a genetic association between the SNP rs580253 Casp1 genotype, rs551684387 Casp1 genotype and the severity of infection COVID-19, and there is no genetic link between the two studied SNPs and severity of infection COVID-19.

Keywords: Coronavirus, Acute Respiratory Syndrome

Introduction

Coronavirus is an RNA virus that consists of 27-32 kb of positive-sense single-stranded RNA. Coronaviruses are classified as alpha, beta, delta, or gamma coronaviruses and belong to the coronaviridiae family.[1,2] When examined under an electron microscope, the spherical external spike protein has a distinct crown appearance, as the name suggests.[3,4] This novel virus causes Coronavirus disease 2019 (COVID-19) which is a respiratory infection that first appeared in late 2019 in Wuhan city of China.[5] Following Severe Acute Respiratory Syndrome (SARS) and Middle-East Respiratory Syndrome (MERS), it is the third coronavirus-borne zoonotic disease to affect humans.[6]

The virus may have used a virus receptor that is primarily expressed in the lungs to cause this extreme appearance.[7] A total of 45,000 cases of pneumonia have been reported from 26 countries, including China, as of February 11, 2020. Approximately 96.8% of all instances have been documented in China, with patients from Hubei province accounting for 75% of all cases.[9] In Iraq, the first case was reported on February 24, 2020 and in Basrah on March 9.[10] People over 60, those in a nursing home or long-term care facility, and those with chronic medical conditions are at a higher risk of developing severe COVID-19 disease.[11] Over-representation in job settings that have higher risks of COVID-19 exposure, economic deprivation (which restricts a person's ability to defend against COVID-19 exposure), neighbourhood disadvantage, and a lack of access to health care are all factors that can lead to an increased burden of COVID-19 in these populations.[12] Caspase-1 was the first in a series of cysteine-dependent aspartate proteases known as caspases that have evolved throughout time. Initially, caspase-1 was found as a protease that in monocytes and microphages proteolytically activates the preforms of interleukin IL-1β and IL-18. Caspase-1, together with caspases 4, 5, 11, and 12, form a subset of inflammasomes.[13] The main caspase-1 substrates found to date are cytokines, which are important mediators of the innate immune response and inflammation.[14] Interleukin1 β is a prototypical proinflammatory cytokine that mediates a variety of effects, including fever, immune cell mobilisation from the bone marrow, and activation of adhesion factors and chemokines, all of which lead to neutrophilic influx at the site of inflammation. IL-1 stimulates T cell development into the Th17 lineage.[15,16] Following activation by a variety of pathogen-associated molecular patterns, IL-1β is primarily produced by monocytes, macrophages, and dendritic cells (DCs) in a nuclear factor kappa-light-chain-enhancer of activated B cell (NF-KB) dependent pathway (PAMPs).[17]

The inflammasome, a multi-protein platform that promotes caspase-1, leading to the proteolytic activity of pro-IL-1β and pro-IL-18 into their mature active forms, is a crucial signalling component of the innate pathway.[18] This SNPs term explains multiple phenotypes which have been used to illustrate the different forms of the same genotype in DNA sequence among individual patients, groups, or populations, sequence repeats, insertions, deletions, and recombination.[19,20] Many polymorphisms found within genes contribute to disease susceptibility and can influence drug responses.[21]

Methods

Eighty blood samples were collected between November 2020 and February 2021, with the age of patients ranging from 20 to 65 years. The sample comprised 50 patients diagnosed with COVID-19 (23 males and 27 females) from the hospitals in Baghdad, and 30 matched apparently healthy subjects as control (20 males and 10 females).

Patients and Controls

Under aseptic conditions, 5 mL of peripheral blood was drawn from patients and apparently healthy control. The patients were selected according to their history recorded by the Iraqi Ministry of Health and Control as per the results of their PCR test.

DNA Extraction

This study includes extracting DNA from whole blood for 80 patients, by using gSYNC DNA extraction kit (Geneaid/ Taiwan) with little optimisation. Quantus fluorometer (Promega, USA) was used to detect the concentration of purified DNA in order to detect the goodness of samples for downstream applications.

Primer Design

These primers were supplied by Microgen Company in a lyophilized form. Lyophilized primers were dissolved in nuclease-free water to give a final concentration of 100 pmol/µl as a stock solution. A working solution of these primers was prepared by adding 10 µl of primer stock solution (stored at -20°C) to 90 µl of nuclease-free water to obtain a working primer solution of 10 pmol/µ.

Application of Polymerase Chain Reaction

The human DNA was detected by Casp 1 gene by using conventional PCR technique and the products of the gene were confirmed by agarose gel electrophoresis in 1.5% agarose that was stained with ethidium bromide. Then electrophoresis was performed at 100 volts for 60 minutes and finally, it was photographed under a UV transilluminator.

DNA Sequencing

Sixty PCR products were sent for Sanger sequencing using ABI3730XL, automated DNA sequences by Macrogen Corporation, Korea. Sanger sequencing is a method of DNA sequencing based on the selective incorporation of chain-terminating dideoxynucleotides by DNA polymerase

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during DNA replication. The results were received by email and then analysed using Geneious software.

Statistical Analysis

Statistical Package for Social Science (SPSS) version 20 program was used to elucidate the differences in parameters. Normality test was used to estimate the normal and non-normal distribution of data, ANOVA test, CShi-square, and Duncan test were used to compare between the studied groups. Hardy-Weinberg Equation, Odd Ratio, Fisher Exact test, and Confidence Intervals were used to compare between the groups and interpret the result after 20 minutes.

Results and Discussion

A total of 50 patients with a confirmed diagnosis of COVID-19 were included in the study. All were positive for SARS-CoV-2 according to the nucleic acid testing by RT–PCR of nasopharyngeal swabs. 30 people with a negative result for SARS-CoV-2 were included in the study as the control group.

Socio-demographic Characteristics

Age

Table 1 shows that the mean ages of the apparently healthy control group and patient group were 37.57 ± 2.07 and 39.02 ± 1.86 respectively. There are nonsignificant differences between patient and control groups (p-value = 0.251).

The samples in the current study were divided into two groups, the first group was between 18-40 years (G1) and the second group was 41 years and above (G2). In the control group, 73.3% of participants belonged to G1 and 26.7% to G2. These percentages were 58% in G1 and 42% in G2 in the patient group. The mild cases in both groups were equal (50%). The moderate cases in G1 and G2 were 59.3% and 40.7% respectively, and the severe cases were 64.29% and 35.71% respectively. There are non-significant differences between all groups included in this study.

The results obtained were in disagreement with a few previous studies, which state that there are significant differences and there is a relationship between age and infection severity, indicating that age is a risk factor and individuals with older ages are at a higher risk of getting infected by COVID-19.[22] Some studies states that the age of the patients was not a risk factor for COVID-19 infection.[23]

Gender

As per the distribution of study subjects according to their age, in the healthy control group, there were 66.7% males, in each COVID group, there were 50% males in mild infection category, 37.04% in moderate category, and 57.14% in severe category, while there were 33.3% females in the control group, 50% females in the mild infection category, 62.96% in the moderate category, and 42.86% in the severe category. There were non-significant differences between the control and patient groups (Table 2).

Table 1.Classification of Participants as per their Age

Age Groups (Years)	Control (N = 30)		PCR positive Patients (N = 50)		Mild (N = 8)		Moderate (N = 27)		Severe (N = 14)	
	No.	%	No.	%	No.	%	No.	%	No.	%
18-40	22	73.3	29	58	4	50	16	59.3	9	64.29
≥ 41	8	26.7	21	42	4	50	11	40.7	5	35.71
χ^2	--------		1.90		1.59		1.20		0.37	
P-value			0.1 NS		0.2 NS		0.2 NS		0.5 NS	

No.: Number, P: Probability, χ^2: Chi-square, NS: Non-significant,Chi-square test was used to differentiate between groups.

Table 2.Classification of Participants as per their Gender

Gender	Control (N = 30)	Mild (N = 8)	Moderate (N = 27)	Severe (N = 14)
Male	20	4	10	8
Percentage (%)	66.7	50	37.04	57.14
Female	10	4	17	6
Percentage (%)	33.3	50	62.96	42.86
χ^2	----------	0.75	5.0	0.37
P-value		0.3	0.02*	0.5

N: Number, P: Probability, χ^2: Chi-square, NS: Non-significant.

* Significant at P < 0.05. Chi-square test was used to differentiate between groups.

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The results obtained were in disagreement with previous studies, in which state there were significant differences between the control and patient group, including the study that was conducted on Italian patients, where the incidence of males was higher than females.[24]

Molecular Study

Detection of Target Genes by PCR

Conventional PCR Results

The result for the Casp1 gene was positive for all isolates as shown in Figure 1.

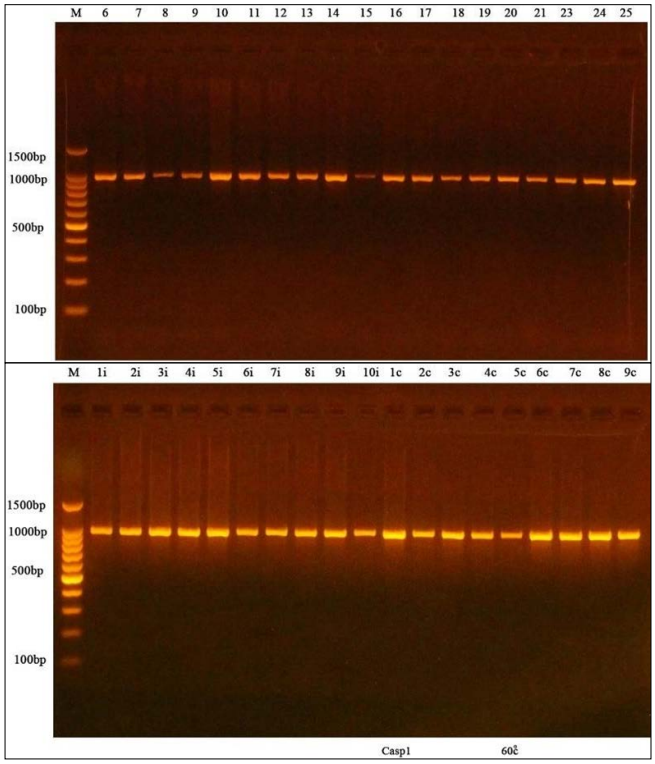

Figure 1.Results of the Amplification of Casp1 Gene of Human Samples Fractionated on 1.5% Agarose Gel Electrophoresis Stained with Eth. Br. M: 100bp Ladder Marker. Lanes 1-19 resemble 961bp PCR products

Innate immune system the first line of defence against microbial pathogens, pathogen-associated molecular patterns (PAMPs) released during infection or endogenous damage-associated molecular patterns (DAMPs) produced during cellular or tissue injury,[25] Immune responses are initiated and perpetuated by molecules derived from microorganisms, pathogen-associated molecular – pattern molecules or from the damage or death of host cells (DAMP). Many DAMPs are nuclear or cytosolic proteins with a defined intracellular function that when released outside the cell following tissue injury, move from a reducing to an oxidizing milieu resulting in their functional denaturation.[26] The main cause of lung infection during a response to SARS-CoV-2 is an increase in these pro-inflammatory cytokines and the dysregulation of the immune response.[27] Gene regulation has an essential role in the host defence against pathogens, and its dysregulation has been demonstrated in different infectious diseases or disease progression.[28]

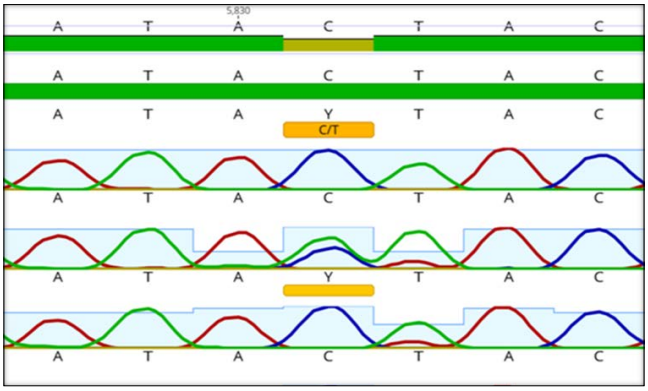

Figure 2.Analysis of rs580253 SNP of Casp1 Gene using Sanger Sequencing. Single "C" peak indicative of a C homozygous allele. Presence of the "C" and "T" peaks indicative of C/T heterozygous allele

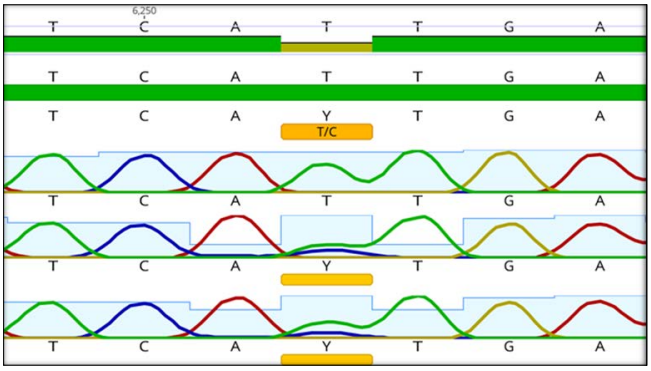

Figure 3.Analysis of rs551684387 SNP of Casp1 Gene using Sanger Sequencing. Single "T" Peak indicative of a T Homozygous Allele. Presence of the "T" and "C" peaks indicative of T/C Heterozygous Allele

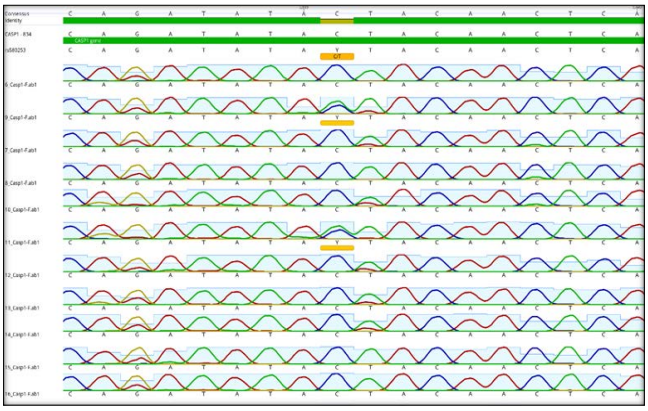

Figure 4.Analysis of rs580253 SNP of Casp1 Gene using Sanger Sequencing. Single "C" Peak Indicative of a CC Homozygous Allele, while "Y " Peak Indicative CT Heterozygous Allele

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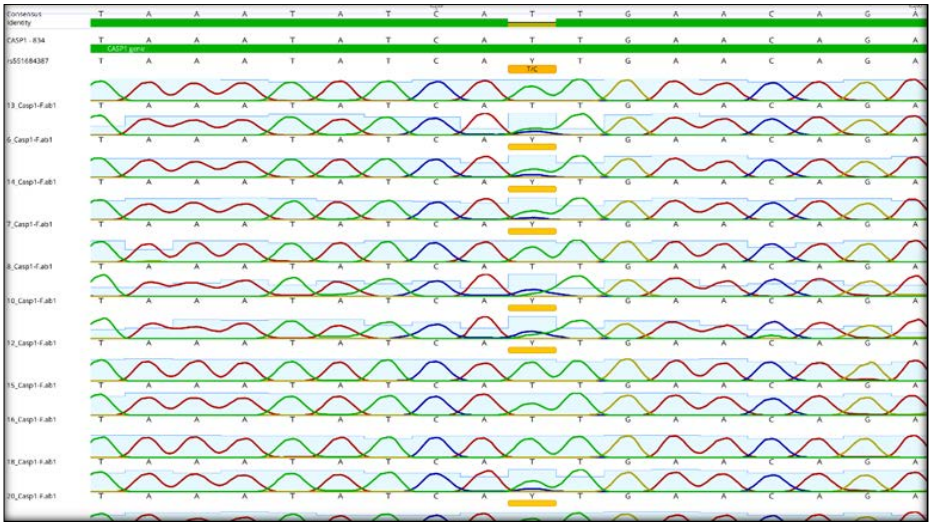

Figure 5.Analysis of rs551684387 SNP of Casp1 Gene using Sanger Sequencing. Single "T" Peak Indicative of a TT Homozygous Allele while "Y " Peak Indicative TC Heterozygous Allele

Table 3.Distribution of Casp1 Genotypes in the Study Groups

Genotypes	Control		Total Patients		Mild		Moderate		Severe	
	Observation	Expectation	Observation	Expectation	Observation	Expectation	Observation	Expectation	Observation	Expectation
CC	18	19	26	27.2	6	5.6	17	15.8	3	2.9
CT	8	7	7	4.8	2	2.4	3	4.2	2	2.1
χ^2	0.19		0.33		0.095		0.4		0.017	
P-value	0.63		0.61		1		0.60		1	
TT	12	12.5	19	20.6	6	5.6	10	11.4	3	2.9
TC	14	13.5	14	12.4	2	2.4	10	8.6	2	2.1
χ^2	0.03		O.34		0.095		0.41		0.017	
P-value	0.8		0.5		1		0.5		1	

Sequencing of Product Amplification for Casp1

60 out of 80 samples (34 patients and 26 control) were analysed by Sanger sequencing to detect the presence of caspases within these sequences. The gene size was 961 base pairs and its location was human chromosome 11. The sequences were compared with the sequences of NCBI Gen Bank primer set covers exon 6 on Casp1 gene.

This study included the importance of the relationship and the association between caspase-1 genotype and patients infected with COVID-19, the comparison of genetic patterns between patients and control, and then linking them according to the severity of the infection. Table 3 shows allelic frequencies of these Casp1 polymorphisms in each study group rs580253 SNP and rs551684387 SNP of Casp1 gene. TT and CC were homogeneous, while TC and CT were heterogeneous.

The homozygous zygote genotype CC in rs580253 SNP was recorded and it was recurrent in the control group (18 out of 26 respondents), and the heterozygous genotype CT was 8 out of 26. In the patient group, the genotype CC was recurrent, 27 out of 34, and the heterozygous genotype CT was 7 out of 34. In rs551684387 SNP, only 46 samples were obtained, while the remaining 14 were not sequenced due to a break in the result reading. Genotype TT was recorded and it was recurrent in the control group (5 out of 26 respondents), and the heterozygous genotype TC was 14 out of 26. In the patient group, the genotype TT was recurrent (12 out of 34), and the heterozygous genotype TC was 15 out of 34.

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Genotypes rs580253 were comparable between the patient and control groups. The p-value was 0.61 and 0.63 respectively, and this indicates the presence of non-significant differences. rs580253 genotypes were comparable between cases. The p-value was 1 for mild cases, 0.60 for moderate cases, and 1 for severe cases. This indicates the presence of non-significant differences. The distribution of rs551684387 genotypes in the control group was in HWE (p = 0.8) and in the patient group, it was 0.5. This indicates the presence of non-significant differences. rs551684387 genotypes were comparable between cases. The p-value for mild and severe cases was 1, and for moderate cases, it was 0.5. This indicates the presence of non-significant differences.

After the statistical analysis of rs580253 Casp1 genotype, it was found that there was no genetic association between the SNPs of the caspase-1 gene and the severity of infection for patients infected with COVID-19 which is not consistent with many of the studies. They stated that the genotype of caspase-1 is related to many diseases and their development.[29,30,31] The results obtained from the analysis of rs551684387 genotypes and the study of their relationship with the severity of infection showed that there was no genetic association between the SNPs of caspase-1 gene and severity of infection for patients infected with COVID-19 because there were no significant differences between them. We did not find any previously published research showing the relationship of this SNAP and its study with any disease condition.

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Conflict of Interest: None

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