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Coronavirus Pandemic

Association of *OAS1* and *MxA* variants with COVID-19 in Pakistani patients

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Abstract

Introduction: Coronaviruses, a family of enveloped RNA viruses, have been implicated in various clinical disorders including coronavirus disease 2019 (COVID-19). Host genetic factors, including the *OAS1* and *MxA* gene variants may have a role in determining susceptibility to viral infections. Understanding the genetic factors involved in unraveling COVID-19's diverse clinical outcomes is critical for disease management. This study investigated the impact of *OAS1 rs2660* and *MxA rs2071430* genotypes on COVID-19 susceptibility and severity among Pakistani patients.

Methodology: This was a comparative cross-sectional study. Fifty patients diagnosed with COVID-19 and 50 controls were recruited and genotyped for the selected gene variants.

Results: The *OAS1* gene *rs2660* exhibited an association with COVID-19 susceptibility in various genetic models. The risk decreased with *AG* genotype (OR = 0.23, 95% CI = 0.09-0.58; $p = 0.0011$) compared to *GG* in codominant models. In dominant (OR = 0.35, 95% CI = 0.15-0.81; $p = 0.013$) and overdominant (OR = 0.21, 95% CI = 0.08-0.53; $p = 0.0005$) models, the single nucleotide variant (SNV) decreased COVID-19 susceptibility risk. There was no association of *OAS1 rs2660* genotypes with COVID-19 severity. We did not find a significant association between *MxA rs2071430* variant and COVID-19 susceptibility.

Conclusions: *OAS1 rs2660 AG* genotype showed decreased risk of COVID-19 susceptibility among Pakistani patients. This study provides insight into the role of the *OAS1* and *MxA* variants in COVID-19. This finding could aid researchers in understanding genetic susceptibility and severity in COVID-19 by identifying at-risk individuals and determining the optimal treatment.

Key words: COVID-19; gene; *MxA*; *OAS1*; Pakistani; variant.

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Introduction

The coronavirus disease (COVID-19) was first noted in Wuhan, China, in December 2019, and declared a pandemic on March 11, 2020. It is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1-3]. Coronaviruses are single-strand, enveloped RNA viruses, with genomic size of approximately 30 kb, and belong to the Coronaviridae family. These viruses have been associated with various clinical disorders, including respiratory, gastrointestinal, hepatic, neurological, hypercoagulability, and endothelial dysfunction [4,5].

SARS-CoV-2 attaches to host cells through the angiotensin-converting enzyme-2 (ACE2) receptor [6]. After endocytosis and eventual uncoating, it uses host cellular machinery to generate new viruses. Subsequently, the exocytosed virions activate the host immune system, releasing cytokines, leading to inflammation and immunological dysfunction by activating or inhibiting immune cells. This may lead to septicemia, shock, multiple organ system failures, and death [4].

Host genetic factors influence susceptibility and modulate the severity of acquiring various infections [7]. The 2′, 5′-oligoadenylate synthetase (OAS)

antiviral protein has been shown to be associated with COVID-19 susceptibility. The chr12q24.13 locus harbors three genes that encode antiviral OAS enzymes (OAS1/2/3) alongside interferon (IFN)-induced antiviral proteins that activate ribonuclease L, which is an essential component of intracellular viral immune response; however, only OAS1 has been proven crucial for anti-SARS-CoV-2 action [8]. Single nucleotide variants (SNVs) of the *OAS1* gene influence *OAS1* expression and enzyme activity, possibly affecting viral infection susceptibility and severity. So far, 57 SNVs of the *OAS1* gene have been documented. Two functional variants (*rs1131454* and *rs2660*) have been linked to the inhibition of viral replication in hepatitis B and C, dengue, influenza A, and SARS-CoV [9].

The antiviral protein Myxovirus resistance A (MxA) influenced by IFN α and β, may inhibit viral replication. Variants found in the *MxA* promoter region have been linked to enhanced promoter function and a modified response to IFN-α and β. These genetic variations in *MxA* could potentially impact an individual's susceptibility to SARS-CoV infection and disease progression [10,11].

This study investigated the impact of *OAS1 rs2660* and *MxA rs2071430* variants on COVID-19 susceptibility and severity among Pakistani patients. This study could aid researchers in understanding genetic susceptibility and severity to SARS-CoV-2 infection, distinguishing at-risk individuals, and determining the optimal treatment.

Methodology

Study design

After obtaining approval from the ethical review committee, this comparative cross-sectional study was conducted at the Molecular Biology and Genetics Laboratory, Liaquat University of Medical and Health Sciences (LUMHS), Jamshoro, Pakistan, in 2021–2022. All participants (cases and controls), or the next of kin of critically ill patients, provided informed consent.

Study participants, sample size, and selection criteria

One hundred male and female participants were recruited for this study. Fifty patients diagnosed with COVID-19 were recruited from isolation wards at LUMHS hospital. SARS-CoV-2 infection was confirmed using the real-time reverse transcription (RT) polymerase chain reaction (PCR) method (RT-PCR) on nasopharyngeal swab samples. Fifty healthy, unrelated, and exposed individuals with negative SARS-CoV-2 RT-PCR from general population were randomly chosen as controls.

The COVID-19 patients were categorized into; mild/moderate (COVID-19 symptoms without dyspnea, or abnormal chest radiography, or lower respiratory disease with $SpO_2 \geq 94\%$) and, severe ($SpO_2 < 94\%$, respiratory rate > 30 breaths per min, $PaO_2/FiO_2 < 300$ mm Hg, or lung infiltrates > 50%) [12].

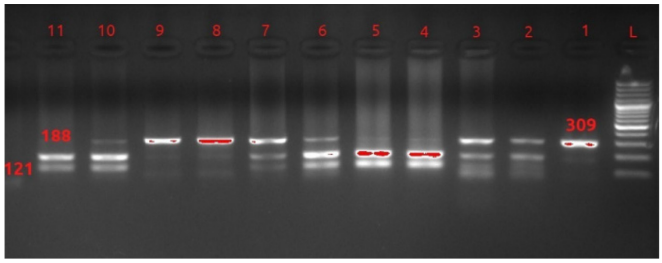
Cases with a negative and controls with a positive SARS-CoV-2 RT-PCR, patients with any other viral illness, and symptomatic controls were excluded from the study.

Molecular detection and statistical analysis

For molecular detection, DNA was extracted from collected blood samples via an inorganic method [13]. The *OAS1* gene *rs2660* is a nonsynonymous SNV (g.chr12:112919637) and corresponds to an Arg397Gly substitution [14,15]; whereas, *MxA rs2071430* is a 5'-UTR G>T variant (g.chr21:41426138). The primer sequences were designed on Primer3web version 4.1.0 (https://primer3.ut.ee/), followed by confirmation through UCSC in-Silico PCR and Blat [16]. The sequence of primers for *OAS1* rs2660 were: forward: 5′-GAGGACTGGACCTGCACCATCCTC-3′; reverse: 5′-AGAAAGTCAAGGCTGGAATTTCAT-3′. The sequence of primers for *MxA* rs2071430 were: forward: TGAAGACCCCCAATTACCAA; reverse: GAAACTCACAGACCCTGTGCTGA.

The primers were optimized by using different buffer concentrations at various annealing temperatures. A PCR mixture of 20 µL comprised of DNA (4µL), dNTPs (2µL), $MgCl_2$ buffer (2µL), 0.6 U *Taq* polymerase, and primers (forward and reverse: 0.6 µL each) was prepared. The desired fragments were amplified using a 2720 thermocycler (Applied Biosystems, Foster City, California, USA). For *OAS1* rs2660, PCR conditions were 95 °C (7 min); 35 cycles at 95 °C (30 s), 58 °C (30 s), 72 °C (30 s); and a final extension at 72 °C (7 min). The PCR amplified products

Figure 1. Agarose gel electrophoresis showing AA 309 bp; GG 188 and 121 bp; and AG 309, 188, and 121 bp fragments of polymerase chain reaction (PCR) amplified DNA digested with *MboII* emzyme.



of 309 bp were digested with the *Mbo*II enzyme (New England Biolabs, Ipswich, Massachusetts, USA) at 37 °C for one hour. Subsequently, the fragments were separated into AA 309 bp; GG 188 and 121 bp; and AG 309, 188, and 121 bp on 2% agarose gel (Figure 1).

The PCR conditions for *MxA* rs2071430 were 94 °C (5 min); 35 cycles at 94 °C (30 s), 58 °C (30 s), 72 °C (1 min); and a final extension at 72 °C (7 min). The PCR products of 296 bp were separated on 1.2% agarose gel and sequenced on ABI PRISM 3130 genetic analyzer (Foster City, California, USA).

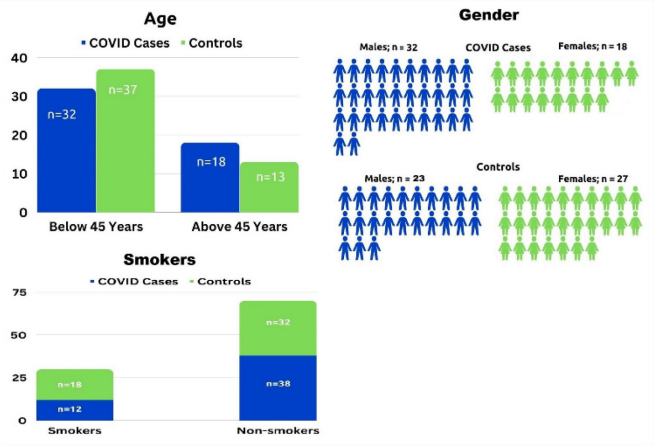
For data analysis, SPSS version 23 (IBM Corp, Armonk, NY, USA) and SNPStat [17] software were used. Frequency/percentage were computed for categorical variables and mean ± standard deviation (SD) for continuous variables. The association of SNV with COVID-19 was calculated by logistic regression analysis at $p < 0.05$ significance.

Results

No difference in age distribution ($p = 0.28$), gender ($p = 0.07$), or smoking status ($p = 0.19$) between controls and cases were found (Figure 2). The majority of the patients in our study presented with symptoms, comorbidities, and raised laboratory biomarkers (Table 1).

The genotype distribution of SNVs was concordant with Hardy-Weinberg equilibrium (HWE) in controls. *OAS1 rs2660* exhibited an association with COVID-19 in various genetic models (Table 2). The risk with genotype AG was lower compared to GG (OR = 0.23, 95% CI = 0.09-0.58; $p = 0.0011$). The SNVs decreased the COVID-19 susceptibility risk under dominant (OR = 0.35, 95% CI = 0.15–0.81; $p = 0.013$) and overdominant (OR = 0.21, 95% CI = 0.08-0.53; $p = 0.0005$) models. No association of *OAS1 rs2660* genotypes with COVID-19 severity was found (Table 3).

Figure 2. Age, gender and smoking status of the COVID-19 cases and controls.



No association between *MxA rs2071430* variant and COVID-19 susceptibility was detected among Pakistani patients.

Discussion

Interindividual response variability to SARS-CoV-2 infection, varying from asymptomatic and mild to lethal disease, necessitates an immediate comprehension of the underlying molecular mechanisms. Genome-wide association study investigating COVID-19 severity and susceptibility have found strong evidence for the interaction of various genomic loci. Strong association of COVID-19-related respiratory failure with *rs11385942* SNVs at the *3p21.31* locus incorporating *CCR9*, *SLC6A20*, *XCR1*, *CXCR6*, *FYCO1*, and *LZTFL1* genes; and with *rs657152 SNV* at *9q34.2* locus corresponding to the

Table 1. Symptoms, comorbidities, and clinical investigations in COVID-19 cases.

Variables			COVID-19 cases
Shortness of breath	Present	n (%)	44 (88)
	Absent	n (%)	06 (12)
Comorbidity	Diabetes	n (%)	12 (24)
	Hypertension	n (%)	14 (28)
	More than one comorbidity	n (%)	15 (30)
	None	n (%)	09 (18)
O_2 Saturation	> 94%	n (%)	16 (32)
	< Lower than 94%	n (%)	34 (64)
D-dimer	Raised	n (%)	31 (62)
	Normal	n (%)	19 (38)
ESR	(mm/1st hour)	Mean ± SD	42.6 ± 30.3
C-reactive protein	(mg/dL)	Mean ± SD	8.77 ± 18.4
Ferritin	(ng/mL)	Mean ± SD	931.6 ± 929.6
LDH	(IU/L)	Mean ± SD	630.2 ± 357.8
Pro BNP	(pg/mL)	Mean ± SD	745.9 ± 717.9

COVID-19: coronavirus disease 2019; ESR: erythrocyte sedimentation rate; LDH: lactate dehydrogenase; Pro BNP: B-type natriuretic peptide; SD: standard deviation.

Table 2. Genotype/allele frequencies and association of the *OAS1 rs2660* and *MxA rs2071430* gene variants with COVID-19.

Genetic model/HWE (*p*)	Allele/Genotype	COVID-19 cases *n* (%)	Controls *n* (%)	OR (95%CI)	*p*
OAS1 rs2660					
Alleles	G	82 (82)	74 (74)	1.00	0.1740
	A	18 (18)	26 (26)	0.62 (0.32–1.23)	
Codominant	GG	37 (74)	25 (50)	1.00	
	AG	8 (16)	24 (48)	0.23 (0.09–0.58)*	0.0011*
	AA	5 (10)	1 (2)	3.38 (0.37–30.68)	
Dominant	GG	37 (74)	25 (50)	1.00	0.013*
	AG-AA	13 (26)	25 (50)	0.35 (0.15–0.81)*	
Recessive	GG-AG	45 (90)	49 (98)	1.00	0.079
	AA	5 (10)	1 (2)	5.44 (0.61–48.40)	
Overdominant	GG-AA	42 (84)	26 (52)	1.00	0.0005*
	AG	08 (16)	24 (48)	0.21 (0.08–0.53)*	
Log-additive	--------	--------	--------	0.64 (0.33–1.25)	0.18
HWE (*p*)	--------	0.0041	0.14	--------	--------
MxA rs2071430					
Alleles	G	99 (99)	100 (100)	1.00	0.4988
	T	01 (1)	0	3.03 (0.12–75.28)	
Genotypes	GG	49 (98)	50 (100)	1.00	0.4966
	GT	01 (02)	0 (0)	3.06 (0.12–76.95)	
HWE (*p*)	--------	1	1	--------	--------

CI: confidence interval; COVID-19: coronavirus disease 2019; HWE: Hardy-Weinberg equilibrium; OR: odds ratio. * represent significant *p* values.

ABO blood group was reported. European association studies have distinguished the *OAS* zone as a COVID-19 risk region [18]. The identified protective Neanderthals-inherited haplotype on chromosome 12 covers the three genes *OAS1*/2/3. The region encodes enzyme-activating proteins for RNA virus infections and confers 22% lower risk of developing severity among COVID-19 patients. However, geographical distribution of the Neanderthal risk haplotype revealed the absence of *OAS1* rs47767027 in East Asian populations [19,20]. Most COVID-19 association studies were conducted in Caucasians, whereas previous SARS genetic studies were primarily performed in East Asians. In the COVID-19 era, host genetic research in populations from South Asia, Africa, and South America remains underreported [21].

This study has reported the *OAS1* rs2660 variant and COVID-19 susceptibility and severity in South Asians and found that the individuals with the AG genotype were protective to COVID-19. A previously reported gene candidate approach that focused on selected target genes identified *rs1143627* (*IL1B* gene) and *rs1131454* (*OAS1* gene) as independent genetic risk factors related to COVID-19 severity among the Japanese, whereas *rs2660* and *rs10774671* had no effect in that study. The mechanism involving disease susceptibility and severity due to different genetic variations among similar genes in different ethnicities may be elucidated to understand the *OAS1* pathway, as hereditary tendency may further cause dysfunction of antiviral innate immune response in COVID-19 patients. In addition to these findings, additional research on the mechanisms underlying COVID-19 pathogenesis may advance novel preventative and therapeutic strategies [22].

OAS genes are IFN-inducible genes that play a crucial role as the initial line of antiviral defense. Preliminary findings from phase III of a clinical trial demonstrated that pegylated interferon1 (pegIFN-1) significantly reduced hospitalization and mortality related to COVID-19. Inhaled type 1 IFNs, IFNβ-1a and IFNα2b, are currently being studied as initial therapies for COVID-19 infection, with impressive outcomes [23,24]. The nonsense-mediated mRNA decay (NMD) targeting the *OAS1* haplotype was linked to lower standard *OAS1* expression, a significantly increased risk for COVID-19 severity, and compromised SARS-CoV-2 clearance. A clinical trial suggested that treatment with IFNs may improve SARS-CoV-2 clearance in relation to specific *OAS1* variants Though these medications improved viral clearance, populations with the *OAS1* risk haplotype (*rs2660-A*,

Table 3. Association of *OAS1 rs2660* gene variant with COVID-19 severity.

***OAS1* genotype**	**Mild/Moderate**	**Severe**	**OR (95% CI)**	***p***
GG	12	25	1.00	----
AG	02	06	1.44 (0.25-8.22)	0.68
AA	02	03	0.72 (0.11-4.89)	0.74

CI: confidence interval; COVID-19: coronavirus disease 2019; OR: odds ratio.

rs1131454-A, and *rs10774671-A*, i.e., AAA) would gain the most from them due to their reduced ability to eliminate the virus in the absence of treatment [8]

We did not find any association of *MxA* gene variant with COVID-19 in our population. *MxA*, a cytoplasmic protein, has demonstrated antiviral action against multiple viruses and genetic variants. Specifically, *rs17000900* and *rs2071430* SNVs at the promoter region, have been linked to increased activity and potential effects on nuclear protein binding [25]. Previous studies have reported an association between the *rs2071430* SNV and SARS-CoV infection, as well as hypoxia resulting from the infection [26,27]. Despite promising initial findings, further investigation into the association between *MxA* and CoV-related phenotypes, employing robust study designs and larger cohorts, especially in COVID-19 patients is necessary.

Though the small sample size is one of our study limitations, the significant association of the *OAS1* gene variant with COVID-19 in our study directs further research to explore the genetic susceptibility and disease severity in larger sample size studies in other populations. Moreover, we recognize the imperative for future investigations to explore the relationship between different COVID-19 variants and genetic variations.

Conclusions

This study provides insight into the role of the *OAS1* and *MxA* variants in COVID-19 among Pakistani population. Moreover, hereditary factors influencing the COVID-19 disease course may provide novel biological perspectives into pathophysiology and distinguish potential therapeutic targets for drug development or repositioning. This finding is important because, even though vaccines are available, treating the disease is still a top priority.

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