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Association of KIR gene polymorphisms with COVID-19 disease

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ABSTRACT

Background: Natural killer (NK) cells play an essential role against viruses. NK cells express killer cell immunoglobulin-like receptors (KIRs) which regulate their activity and function. The polymorphisms in KIR haplotypes confer differential viral susceptibility and disease severity caused by infections. We investigated the association between KIR genes and COVID-19 disease severity.
Methods: 424 COVID-19 positive patients were divided according to their disease severity into mild, moderate and severe. KIR genes were genotyped using next generation sequencing (NGS). Association between KIR genes and COVID-19 disease severity was conducted and significant correlations were reported.
Results: In the COVID-19 patients, KIR Bx genotype was more common than AA genotype. The Bx genotype was found more frequently in patients with mild disease, while in severe disease the AA genotype was more common than the Bx genotype. The KIR2DS4 gene carried the highest risk for severe COVID-19 infection (OR 8.48, pc= 0.0084) followed by KIR3DL1 (OR 7.61, pc= 0.0192).
Conclusions: Our findings suggest that KIR2DS4 and KIR3DL1 genes carry risk for severe COVID-19 disease.

1. Introduction

Coronavirus disease 2019 (COVID-19), caused by infection with severe acute respiratory syndrome 2 virus (SARS-CoV-2), has caused considerable morbidity and mortality at an unprecedented scale globally. Since the emergence of the disease, striking heterogeneity in clinical presentations and outcomes following infection has been observed, ranging from silent or benign infection to critical pneumonia requiring intensive care [1]. Epidemiologists rapidly identified older age, male sex and pre-existing comorbidities as major risk factors for disease progression [2]. These factors, however, do not fully explain the clinical variability in response, and evidence indicates the involvement of innate immune system components in modulating COVID-19 presentation [3].

Natural killer (NK) cells are innate effector lymphocytes that are typically divided into two phenotypically and functionally distinct subsets: $CD56^{bright}CD16^{-}$ and $CD56^{dim}CD16^{+}$ [4]. The $CD56^{dim}CD16^{+}$ NK cells express the killer cell immunoglobulin-like receptor (KIR), and are highly cytotoxic, while $CD56^{bright}CD16^{-}$ NK cells are the major producers of cytokines [4]. It is well established that NK cells have a direct role in protection against viral infections [5]. In humans, NK cells have been shown to rapidly respond during the acute phase of multiple infections including influenza A virus, dengue virus, cytomegalovirus

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and hepatitis C [6–9]. Interestingly, recent work has shown that NK cell numbers are increased at the site of SARS-CoV-2 infection and preliminary evidence suggests links between NK cells and COVID-19 severity [10,11].

KIRs are a family of highly polymorphic type 1 transmembrane glycoproteins that convey inhibitory or activating signals to subpopulations of NK cells and T lymphocytes upon recognition of their ligands, which are primarily human leukocyte antigen (HLA) class I allotypes [12]. KIRs are encoded by a set of highly polymorphic genes located within the leukocyte receptor complex on chromosome 19q13.4 [13]. To date, fourteen KIRs triggering either inhibition (3DL1–3, 2DL1–3, 2DL5) or activation (3DS1, 2DS1–5), or both (2DL4) have been described [13]. Inhibitory receptors are critical for self-tolerance. Their binding to self-HLA class I ligands sends inhibitory signals preventing cytolysis, and down-regulation of self-HLA class I ligands due to viral infection blocks inhibitory signals and leads to lysis of target cells. Activating receptors on the other hand bind to self-altered ligands that are expressed on cell surfaces due to cell stress or damage. This induces NK activation signals and leads to lysis of mainly virally infected or transformed cells [14,15].

Based on the gene content, two haplotypes (A and B) and genotypes (AA and Bx, where x can be A or B) have been described for KIR. The group A haplotype encodes inhibitory KIRs for all four HLA class I ligands and a single activating KIR expressed on NK cells [16]. The group B haplotype has a variable gene content with additional activating KIR genes and exhibits a stronger response to virally infected cells [17,18]. This diversity in KIR affects NK cells activity and susceptibility to several diseases [16]. Given that variations in KIR may contribute to the heterogenous response to SARS-CoV-2 infection, we sought to investigate the influence of genes encoding KIRs on the severity of COVID-19 in a Saudi Arabian population.

2. Materials and Methods

2.1. Subject selection

The study recruited 424 mainly Saudi patients (392 Saudi 92.5%, 32 non-Saudi, 7.5%) with confirmed COVID-19, as defined as positive for SARS-CoV-2 viral RNA by polymerase-chain-reaction (PCR) test from nasopharyngeal swabs or lower respiratory tract samples including endotracheal aspirate, bronchoalveolar lavage fluid or sputum. Patients were recruited from King Abdulaziz Medical City (KAMC) Ministry of National Guard – Health Affairs (MNGHA) in Riyadh and from the Ministry of Health Quarantine Facility in Makkah. Patients were categorized into three groups, based on disease severity. One hundred and thirty-four patients were asymptomatic or with mild disease (asymptomatic were those patients who tested positive by PCR but had no symptoms consistent with COVID-19; mild diseases were those patients with various signs and symptoms of COVID-19 such as fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell but did have shortness of breath or abnormal chest imaging. Ninety-five patients were with moderate disease (patients requiring hospital admission and evidence of lower respiratory disease during clinical assessment or imaging. One hundred and ninety-five patients were with severe disease (patients requiring ICU admission and/or invasive mechanical ventilation). The asymptomatic and mild patients' groups were merged and labelled as "Mild" for simplicity.

2.2. Controls

A total of 260 healthy Saudi individuals were typed for KIR genotypes and were used as the control group. These were registered unrelated stem cell donors with age range of 18–50 years and F:M ratio 110:150. They were collected before COVID-19 and were used to reflect the distribution of KIR gene polymorphisms in the Saudi population.

Table 1
Distribution of disease severity by gender and age.

Severity	Gender		
	Female	Male	Total
Mild (N)	62 (46.27)	72 (53.73)	134 (100)
Mean age (SD)	38.85 (16.45)	35.79 (15.93)	37.21 (16.18)
Moderate (N)	38 (40)	57 (60)	95 (100)
Mean age (SD)	57.18 (17.17)	55.63 (14.47)	56.25 (14.47)
Severe (N)	71 (36.41%)	124 (63.59%)	195 (100)
Mean age (SD)	64.62 (12.88)	62.24 (15.47)	63.11 (14.59)
Total (N)	171 (40.33%)	253 (59.67%)	424
Mean age (SD)	53.63 (19.04)	53.06 (18.97)	53.29 (18.98)

Chi2(2) = 3.2131 $p = 0.201$ for disease severity against gender.
NPtrend$<$0.001 for correlation between the degree of disease severity and age.

2.3. Data collection

Ethical approval for this study and all experimental protocols was obtained from the Institutional Review Board (IRB) at King Abdullah International Medical Research Center (KAIMRC), Ministry of National Guard – Health Affairs (MNGHA) in Riyadh and site-specific approval was obtained from all participating centers. Written informed consent for clinical genotyping and participation in this study was obtained from all patients or their guardians upon recruitment. Detailed demographic information and clinical data were collected from all 424 recruited patients and entered into a secure REDCap electronic data capture tool hosted at KAIMRC. Demographics composed of different factors such as gender, age and nationality. Clinical data comprised vital signs and disease manifestations including fever, cough, dyspnea, diarrhea and chest pain.

2.4. Sample collection, DNA analysis and KIR genotyping

Blood samples were collected in EDTA tubes from all 424 patients infected with SARS-CoV-2 and genomic DNA was extracted from peripheral blood using the Gentra Puregene Blood Kit according to the manufacturer's instructions. The yield of the DNA was then quantified using NanoDropTM spectrophotometer using standard procedures before genotyping. KIR genes (absence/presence) genotyping was performed by next generation sequencing (NGS) using the Illumina NGS platform at the laboratories of Histogenetics (Ossining, NY). Briefly, 64 amplicons were generated for 16 KIR genes by 6 reactions of gene-specific or group-specific multiplex PCR, consisting of three to six amplicons for each gene. Illumina NGS data was analyzed by Multiplex KIR genotyping algorithm developed by HistoGenetics (using IMGT KIR database v2.6.0), and each KIR gene was shown as present or absent. KIR analysis was performed by identifying the presence/absence of each gene in a given sample. Each gene result was dependent on one or more amplicon results. The user analyzed and saved all amplicons present in the amplicon list. Presence/absence of each gene was determined by patterns of amplicons results. The gene result was confirmed in at least two amplicons. After all amplicon results were confirmed, the gene result was automatically assigned by Histo-S.

2.5. Statistical analysis

The STATA software, version 16.0 (StataCorp, College Station, TX, USA) was used for statistical analysis. Characteristics of the study population were examined and stratified by KIR haplotypes and disease severity using descriptive statistics for age and gender. Chi-square test was employed to assess the statistical significance of differences in proportions of KIR haplotypes. Age was expressed as mean values ± SD. Associations between the frequencies of different KIR genes in disease severity versus controls were reported as Odds Ratio (OR) with 95%

Table 2
Comparison of KIR gene frequencies in COVID-19 patients ($N = 424$), disease severity subgroups, Mild ($N = 134$), Moderate ($N = 95$), severe ($N = 195$) and controls ($N = 260$).

			Controls (N = 260)	Total Covid (N = 424)		Mild (N = 134)		Moderate (N = 95)		Severe (N = 195)	
Inhibitory/ Activation	Haplotype A/ B	Gene	N (%) + ve	N + ve	OR(95% CI, p)	N (%) + ve	OR(95% CI, p)	N (%) + ve	OR(95% CI, p)	N (%) + ve	OR(95% CI, p)
I	A	2DL3	215(82.69)	362 (85.38%)	1.22(0.78–1.90, 0.3481)	116 (86.57)	1.35(0.73–2.59, 0.3201)	82(86.32)	1.32(0.65–2.81,0.4136)	164(84.1)	1.11(0.65–1.90, 0.6898)
A	A	2DS4	239(91.92)	417 (98.35%)	5.23(2.10–14.76, <0.0001)[a]	130 (97.01)	2.86(0.93–11.66, 0.05)*	94(98.95)	8.26(1.29–345.08, 0.0151)*	193 (98.97)	8.48(2.03–75.24, 0.0007)[b]
I	C	2DL1	255(98.08)	410 (96.7%)	0.57 (0.16–1.17, 0.2868)	129 (96.27)	0.51(0.11–2.24, 0.2796)	91(95.79)	0.45(0.09–2.31, 0.2248)	190 (97.44)	0.75(0.17–3.29, 0.6444)
I	A	3DL1	241(92.69)	417 (98.35%)	4.70(1.85–13.38, 0.0002)[c]	130 (97.01)	2.56(0.82–10.55, 0.083)	94(98.95)	7.41(1.14–311.08, 0.0236)*	193 (98.97)	7.61(1.79–67.94, 0.0016)[d]
P	C	2DP1	255(98.08)	410 (96.70%)	0.57(0.16–1.17, 0.2868)	129 (96.27)	0.51(0.11–2.25,0.2796)	91(95.79)	0.45(0.09–2.30, 0.2248)	190 (97.44)	0.75(0.17–3.29, 0.6444)
I	B	2DL2	164(63.08)	243 (57.31%)	0.79(0.57–0.09,0.1359)	80(59.7)	0.87(0.55–1.36, 0.5133)	52(54.74)	0.71(0.43–1.17, 0.1541)	111 (56.92)	0.75(0.50–1.11, 0.1343)
I	B	2DL5	166(63.85)	234 (55.19%)	0.70(0.51–0.97, 0.0257)*	80(59.7)	0.84(0.54–1.32, 0.4209)	44(46.32)	0.49(0.30–0.81, 0.0029)[e]	110 (56.41)	0.73(0.49–1.09, 0.1081)
A	B	2DS1	104(40)	129 (30.42%)	0.66(0.47–0.92, 0.0103)*	42(31.34)	0.69(0.43–1.09, 0.0919)	29(30.53)	0.66(0.38–1.12, 0.1026)	58(29.74)	0.64(0.42–0.96, 0.0238)*
A	B	2DS2	164(63.08)	243 (57.31%)	0.79(0.57–1.09,0.1359)	80(59.7)	0.87(0.55–1.36, 0.5133)	52(54.74)	0.71(0.43–1.17, 0.1541)	111 (56.92)	0.77(0.52–1.15, 0.184)
A	B	2DS3	114(43.85)	157 (37.03)	0.75(0.54–1.05, 0.0768)	52(38.81)	0.81(0.518–1.27, 0.3371)	25(26.32)	0.46(0.26–0.79, 0.0027)[f]	80(41.03)	0.89(0.60–1.32, 0.5472)
A	B	2DS5	94(36.15)	122 (28.77%)	0.71(0.51–1.01, 0.0438)*	40(29.85)	0.75(0.47–1.20, 0.2109)	29(30.53)	0.78(0.45–1.32, 0.3239)	53(27.18)	0.66(0.43–1.00, 0.0428)*
A	B	3DS1	98(37.69)	119 (28.07%)	0.65(0.46–0.90, 0.0086)*	41(30.6)	0.73(0.45–1.16, 0.1626)	24(25.26)	0.56(0.32–0.97, 0.029)*	54(27.69)	0.63(0.41–0.96, 0.0252)*
I	AA		68(26.15)	136 (32.08%)	1.33(0.93–1.91, 0.1003)	35(26.12)	1.00(0.60–1.64, 0.9941)	34(35.79)	1.57(0.92–2.67, 0.0757)	67(34.36)	1.48(0.97–2.26, 0.0580)*

I = inhibitory, A = activating, p = pseudogene. A = member of haplotype A, B = member of haplotype B, C = member of both haplotype A and B.
Corrected p values (Pc).
[a] $p < 0.001$.
[b] $p = 0.0084$.
[c] $p = 0.0024$.
[d] $p = 0.0192$.
[e] $p = 0.0348$.
[f] $p = 0.0324$.
* $p > 0.05$.

Table 3
Distribution of KIR haplotypes in the COVID-19 patients by gender.

	Gender		
Haplotype	Female N (%)	Male N (%)	Total
AA	56 (32.75)	80 (31.62)	136 (32.08)
Bx	115 (67.25)	173 (68.38)	288 (67.92)
$Chi^2(1) = 0.0596$	$p = 0.807$		

Table 4
Distribution of COVID-19 disease severity by KIR haplotype.

	Haplotype		
Severity	AA	Bx	Total
Mild N (%)	35 (25.74)	99 (34.38)	134 (31.60)
Moderate N (%)	34 (25.00)	61 (21.18)	95 (22.41)
Severe N (%)	67(49.26)	128 (44.44)	195 (45.99)
$Chi^2(2) = 3.25$	$p = 0.197$		

confidence interval (CI). *P*-value of less than 0.05 was considered significant. For calculating age trend with severity (Pearson's correlation test) using the "nptrend" command in Stata was used. *P*-values of <0.05 after Bonferroni correction for multiple testing were considered significant.

3. Results

The present study consisted of 424 patients with COVID-19-positive PCR. Of the 424 patients, 253 were males and 171 were females. The age range of the patient cohort was 15–104 years with a mean age of 53.29 (Table 1). There was a significant correlation between the degree of disease severity and age (NPtrernd<0.001) (Table 1). The analysis showed no statistical significant association between gender and disease severity, however, there was a gradual increase in the percentage of males with disease severity with decreasing percentage in females with disease severity. In total, more males were positive for COVID-19 (60%) compared to females (40%).

Table 2 shows the distribution of different KIR genes and their frequencies in cases and controls. Genes making haplotype A were more common in both cases and controls than genes making up haplotype B. Haplotype A genes' frequency in controls ranged from 83 to 98% and in cases from 85 to 98%. Haplotype B genes' frequency in controls ranged from 36 to 63% and in cases from 28 to 57%.

The KIR2DS4 gene carried the highest risk in the total group (OR 5.23(95% CI 2.10–14.76, $p < 0.0001$) and the frequency of KIR2DS4 was associated with increasing risk for disease severity (Table 2), reaching an OR of 8.48 in the severe group (95% CI 2.03–75.24, $p = 0.0007$, pc = 0.0084). This was followed by KIR3DL1 which ranked second in risk for the total COVID-19 cases (OR 4.70, 95% CI 1.85–13.38, $p = 0.0002$, pc = 0.0024). Again, KIR3DL1was associated with an increased risk of severity, reaching an OR of 7.61 (95% CI 1.79–67.94, $p = 0.0016$, pc = 0.0192) in the severe group. On the other hand, KIR2DL5, KIR2DS1, KIR2DS5 and KIR3DS1 genes were associated with a protective effect from risk of COVID-19 in the total group (Table 2), although only KIR2DL5 and KIR2DS3 were significantly associated with protection after correction for multiple testing. No statistical significant trend was noticed in the association of these KIR genes and severity. However, it should be noted that both KIR2DS4 and KIR3DL1 are highly frequent in the general population 91.92% and 92.69, respectively.

In the COVID-19 patients, KIR Bx genotype was more common than AA genotype (68% vs 32% respectively), irrespective of gender (Table 3). Table 4 shows the distribution of KIR genotypes with disease severity. The Bx genotype was found to be more frequent in mild disease cases compared to the AA genotype (34.38% vs 25.74%), while in severe disease cases the AA genotype was more common than the Bx genotype (49.26% vs 44.44%) but these differences did not reach statistical significance (Table 4).

4. Discussion

A better understanding of the genetic factors underlying the extremely heterogeneous phenotypic response to infection with SARS-CoV-2 in humans is crucial for both future diagnostics and the development of treatment options. To our knowledge, this is the first published study to date to explore the association between KIR genes and COVID-19 in the Saudi population.

Our data show an association between KIR2DS4 and KIR3DL1, which are part of the inhibitory KIR A haplotype, and increased risk for COVID-19 disease severity. Both KIR3DL1 and KIR2DS4 define the Telomeric A (telA) haplotype. Haplotype A is known for its inhibitory function, and while KIR3DL1 is an inhibitory receptor, KIR2DS4 has activating ability. It was shown that human NK cell receptor KIR2DS4 binds a conserved bacterial epitope presented by HLA-C*05:01, leading to stimulation of $KIR2DS4^+$ NK cells [19]. KIR2DS4 also binds HLA-A11 [20], while KIR3DL1 binds to Bw4 epitopes. A recent study by Bernal et al. [21] found that KIR2DS4 was associated with severe COVID-19 disease only. This is in contrast to what we found in our study, where KIR2DS4 and KIR3DL1 were associated with mild, moderate and severe disease, with increasing risk for disease severity. Thus, implicating KIR2DS4 and KIR3DL1 in susceptibility to COVID-19 disease severity although both genes are highly frequent in the general population.

Homozygosity for the KIR AA genotype was shown to be associated with HBsAg carriage [22]. In addition, KIR2DS4 was found to be associated with increased risk for chronic HBV infection [23]. These data suggest that haplotype A might be associated with risk of chronic HBV infection. KIR2DS4 also plays a major role in the pathogenesis of HIV-1 chronic infection, probably through the maintenance of an excessively pro-inflammatory state [24]. We hypothesize the same mechanism for KIR2DS4 and its association with risk for COVID-19 disease severity.

Leite et al. investigated the immunogenetics of COVID-19 and found that after correction for multiple testing, there was a positive association of the inhibitory genotype AA and KIR2DL3 with daily death rates and a negative association of the stimulatory KIR2DS2 with daily death rates. KIR2DL3 is part of haplotype A, which in our study was positively associated with the risk of severe disease. However, KIR3DL1 was associated with Daily Death Rates [25] but KIR2DS4 was not investigated. Our results showed a positive association between KIR2DL3 and a negative association between KIR2DS2 and COVID-19 disease, however, these associations did not reach statistical significance.

In HIV infection, the KIR3DL1 gene and HLA-B subtypes appear to control NK responsiveness against HLA-negative targets and autologous HIV-infected CD4+ T cells [26]. In patients from Burkina Faso, KIR2DS4 was associated with HIV-1infection, while KIR3DL1 gene was associated with protection against HIV-1 infection [27].

The KIR haplotype A was found to be associated with bronchiolitis obliterans syndrome after lung transplantation but not with cytomegalovirus reactivation [28]. Because NK cells containing the homozygous KIR haplotype A express a phenotype mainly encoded by inhibitory KIRs, this KIR haplotype should be associated with less reactivity against donor cells recognized on lung allografts, and thus absence from Bronchiolitis obliterans syndrome (BOS), instead of the association found in the present study. The KIR AA genotype was found to be associated with BK virus associated nephropathy in kidney transplant patients [29].

These studies indicate that the KIR2DS4 and KIR3DL1 genes have contrasting functionality, but in case of COVID-19 disease, both appear to carry increased risk for severe disease. It should be noted that this study is confined mostly to the Saudi population. KIR genotypes have been shown to be highly variable among different ethnic groups [30]. Our study is focused solely on KIR genes; however, other confounding factors may influence the response to COVID-19 and await discovery in future studies. In addition, our study utilized healthy controls collected

before the pandemic, those were unrelated stem cell donors. They are young compared to our COVID-19 cohort. In conclusion, despite the relatively small sample size of our study, our findings suggest that KIR2DS4 and KIR3DL1 genes are associated with severe COVID-19 disease. Further studies on KIR and COVID-19 are needed to confirm these findings in a larger sample size and using age matched controls.

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Declaration of Competing Interest

The authors declare no conflict of interest.

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