Relationship between KIR genotypes and HLA-ligands with SARS-CoV-2 infection in the Saudi population

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ABSTRACT

Aim: To ascertain whether killer cell immunoglobulin-like receptors (KIR) genes polymorphisms and HLA-I ligands are associated with COVID-19 in Saudi Arabia.
Methods: Eighty-seven COVID-19 patients who tested positive for SARS-CoV-2 and one hundred and fourteen healthy controls were enrolled in this study for genotyping of the 16 KIR genes, HLA-C1 and -C2 allotypes and HLA-G 14-bp indels polymorphisms using the sequence specific primer polymerase chain reaction (SSP-PCR) method. KIR genotype frequency differences and combination KIR-HLA-C ligand were tested for significance.
Results: Framework genes KIR2DL4, KIR3DL2, KIR3DL3, and KIR3DP2 were present in all individuals. The frequencies of KIR2DL2 and KIR2D4 were higher in COVID-19 positive patients than in healthy individuals. The frequencies of the combination KIR2DL2-HLA-C2 was also significantly higher in patients affected by COVID-19 compared with healthy controls.
Conclusion: It was found that the inhibitory KIR2DL2 gene in isolation or combined with its HLA-C2 ligand could be associated with susceptibility to COVID-19 in the Saudi population.

1. Background

Coronavirus disease 2019 (COVID-19) is an infectious disease which is caused by the most recently detected strain, SARS-CoV-2. This highly contagious infection is associated with severe manifestations such as acute respiratory syndrome, cytokine storms and multisystem inflammatory syndrome (Castagnoli et al., 2020; Salata et al., 2020).

The World Health Organization declared the novel coronavirus as a pandemic in March 2020. On a global scale, by the end of April 2021, over 153,000,000 infected people and over 3,206,000 have been reported (Muhareb and Giacaman, 2020). Since the first Saudi Arabian case was reported in March 2020, the total number of confirmed cases had reached 420,000 by the end of April. Among these, 6992 patients were deceased (COVID19 statistics, Ministry of Health, Kingdom of Saudi Arabia. MOH (2021) May https://covid19.moh.gov.sa).

In the course of viral infections, both innate and adaptive immune cells work in unison to promote an effective immune response. Natural killer (NK) cells are cytotoxic lymphocytes. These have the capacity to identify and eliminate tumor and virus-infected cells without prior sensitization using a panel of receptors that interact with ligands, mainly the Human Leukocyte Antigens (HLA), which are expressed at the surface of target cells (Ahlenstiel et al., 2008; Béziat et al., 2013). The KIR gene family, located on human chromosome 19q13.4, includes 15 functional genes (2DL1-4, 2DL5A, 2DL5B, 2DS1-5, 3DL1-3 and 3DS1), and 2

pseudogenes (2DP1, 3DP1). They are organized within a multi-gene family and characterized by their genetic diversity including gene content, copy number variation and also allelic polymorphism (Yawata et al., 2006). According to the number of external immunoglobulin domains (2D or 3D) genes have been divided into the following distinct groups: the inhibitory KIRs (2DL, 3DL) characterized by the presence of a long cytoplasmatic tail with two immune tyrosine-based inhibitory motifs (ITIM), and activating KIR receptors (2DS, 3DS) allowing the transmission of an inhibitory signal and characterizes by the presence of short cytoplasmatic tails corresponds (Selvakumar et al., 1997; McVicar and Burshtyn, 2001).

The genetic diversity of KIRs includes variations in gene content and copy number in addition to allelic polymorphisms + – (Middleton and Gonzelez, 2010).

These receptors did not undergo somatic modifications and remain at the germinal state. For that, they are placed at the interface between innate and adaptive immunity (Vivier et al., 2011).

Molecules of the HLA (or human major histocompatibility complex; MHC), mainly those of class I, play a crucial role in the control of activation or inhibition of the NK cells killing process through a mechanism of missing or altered self (Ljunggren and Kärre, 1990; Sivori et al., 2019).

Interactions with HLA ligands at the surface of target cells implies some surface receptors at the surface of NK cells (Jamil and Khakoo, 2011a; Pierce et al., 2020). The combination of HLA class-I and KIR receptor could influence NK cells and induce immune tolerance (Cao et al; Xu et al., 2020). Studies have revealed that patients with specific HLA alleles are at risk for viral infections including SARS (Sun and Xi, 2014). The relationship between HLA–KIR and cytokine storm have been detected in different diseases caused by viruses including: Spanish flu (Kobasa et al., 2007), severe influenza virus infections (La et al., 2011), dengue virus (Björkström et al., 2011) and hepatitis C infection (Fitzmaurice et al., 2015). Consequently, the diversity of HLA-KIR and their selection of ligand and pathogen-mediated activity have a strong influence on the efficiency of the immune response and then switch of disease toward clearance or severity explaining the occurrence of high mortality rate (Jamil and Khakoo, 2011b; Jost and Altfeld, 2013). It is worth mentioning that in the Saudi population, the associations between KIRs and some cancer or autoimmune diseases have recently been reported (Al Omar et al., 2015; Alomar et al., 2017; Osman et al., 2017).

Many studies have reported that NK cell frequency can fluctuate with moderate and severe disease in peripheral blood and at the site of infection (Wang et al., 2020). Nevertheless, a comprehensive understanding of the NK cell landscape during the infection with SARS-CoV-2 has not yet been determined. While they were widely explored for their roles in many viral infections, their involvement in the host reaction against SARS-CoV-2, has not been sufficiently investigated (Maucourant et al., 2020).

Due to the major role of NK cells in the early immune response against viruses, in the present study, the relationship between some individual KIR receptors is investigated in point of fact as the most important receptor expressed on NK cells, KIR genotype polymorphism and their corresponding ligand of its combinations with the HLA-G and HLA-C1 and -C2 with Covid-19 infection in Saudi Arabia.

2. Materials and methods

2.1. Subjects

2.1.1. Subjects

One hundred and fourteen healthy controls (mean aged 47 ± 11.7 years) and eighty-seven COVID-19 patients (median age,

58 ± 16 years), positive for SARS-CoV-2 were involved in the present study. Peripheral blood samples from all of the participants were collected in EDTA blood collection tubes. All patients and controls gave informed consent and agreed to provide blood samples for a case–control study. Written informed consent was obtained from all the study subjects.

Number of subjects	Patient mean ± STD 87	Control mean ± STD 114
Age (yrs)	58 ± 16	47 ± 11.7

2.2. Genomic DNA extraction and KIR, HLA-C and HLA-G 14-bp typing

Genomic DNA was extracted from peripheral blood using a DNeasy Blood & Tissue Kit (Qiagen, Valencia, CA) according to the manufacturer's instructions. The concentration and purity of each DNA sample were determined using the Nano Drop™ 2000/2000c Spectrophotometers (Thermo Scientific®, USA). The samples were labeled and stored at −20 °C.

Genotyping of KIRs was performed, for 16 genes using the polymerase chain reaction (PCR)-sequence-specific primer PCR-SSP method. To permit the detection of all known KIR genes, HLA-C1 and HLA-C2 the same primers were used as described by (Tajik et al., 2009) which allows for the detection of all known KIR genes.

For HLA-G 14-bp insertion/deletion polymorphism genotyping within the 3′UTR of exon 8 was performed using the primers GE14HLAG (5′-GTGATGGGCTGTTTAAAGTGTCACC-3′) and RHG4 (5′- GGAAGGAATGCAGTTCAGCATGA-3′) (Hviid et al., 1999).

All PCR reactions were performed with the thermocycler apparatus T100™ (Bio-Rad, United States). The PCR products were analyzed by electrophoresis in 2 % agarose gels stained with ethidium bromide and visualized on a UV transilluminator using a gel documentation system (BioRad Gel225 DocXR +) to check for the presence or absence of gene-specific amplicons.

2.3. Statistical analysis

The frequency of each KIR, HLA-C ligand, and KIR/HLA-C ligand combination and insertion/deletion polymorphisms in HLA-G alleles in the patient and control groups were determined by direct counting. Multiple logistic regression models were performed to estimate odds ratios (ORs), confidence intervals (CIs) at 95 % and P values for five inheritance models including, codominant, dominant, recessive, overdominant and log-additive. The Fisher exact test was used when the numbers of genotype and allele are less than 5. Data analysis was performed using SigmaPlot version 11 software and SNPstats (Sole et al., 2006). Hardy–Weinberg equilibrium (HWE) for both the patient and control groups was estimated using SNPStats. The statistical significance was defined as p less than 0.05. Bonferroni correction was used for multiple comparisons. The Akaike information criteria (AIC) was used to select the best fitted model.

3. Results

The present study is the first to attempt the characterization of the KIR, HLA-C1/C2 and HLA-G 14 bp indel polymorphism patterns and its effects on COVID-19 infection among the Saudi population. In this study, 87 COVID-19 positive patients and 114 healthy controls were successfully genotyped for 16 KIR genes, HLA-C1/C2 allotypes and HLA-G 14 bp insertion deletion using sequence-specific PCR amplification method. All framework genes were

detected in both patients and control groups. A significant increase of 2DL1 and 2DS4 genes among patients was observed (OR = 12.07; P = 0.0022) and (OR = 10.15; P = 0.0076) respectively. These genes occur in all patients and with lower frequency in healthy control. For the rest of genes, no significant differences between groups were detected (Table 1).

In this study, the frequency of HLA-C allotypes, which are the main ligands of KIR receptors, were also examined. The two main

allotypes, HLA-C1 and -C2 frequency were determined for both COVID-19 patients and healthy controls. Distributions of HLA-C1C1 genotypes in control ad patients show slightly deviated from HWE ($\chi 2$ = 5.48, p = 0.019). Table 2, shows the relationship between HLA-C1C2 allotypes and genotype for codominant, dominant, recessive, over-dominant and additive genetic models with SARS-CoV-2. Significant association were observed for C1C1 genotype in codominant model and the protective effect against

Table 1
Comparison of KIR gene frequencies between COVID-19 patients and controls.

Genes	COVID-19 No. (%)	HEALTHY No. (%)	OR	CI 95 %	χ^2	P
3DL2	87(100 %)	114(100 %)	NA	NA	NA	NA
3DL3	87(100 %)	114(100 %)	NA	NA	NA	NA
2DL4	87(100 %)	114(100 %)	NA	NA	NA	NA
3DP1	87(100 %)	114(100 %)	NA	NA	NA	NA
2DL1	87(100 %)	101(88 %)	**12.07**	**1.55–93.7**	**8.03**	**0.0022**
2DL3	73(84 %)	94(82 %)	1.10	0.52–2.34	0.01	0.85
3DL1	85(97.7 %)	106(92 %)	3.2	0.66–15.5	0.02	0.19
2DS4	87(100 %)	103(90 %)	**10.15**	**1.29–79.64**	**6.97**	**0.0076**
2DL2	44(50 %)	67(59 %)	0.71	0.40–1.25	1.03	0.31
2DL5	41(47 %)	67(59 %)	0.62	0.35–1.09	2.24	0.11
2DS1	24(27.5 %)	35(31 %)	0.85	0.46–1.59	0.11	0.64
2DS2	37(42 %)	64(56 %)	0.57	0.32–1.01	3.13	0.064
2DS3	40(46 %)	51(44.7 %)	1.05	0.60–1.84	0.001	0.88
2DS5	23(26 %)	33(29 %)	0.88	0.47–1.64	0.06	0.75
3DS1	18(20.6 %)	24(21 %)	0.97	0.49–1.94	0.98	1
2DP1	86(99 %)	114(100 %)	0.37	0.033–4.23	0	1

NA: Non-attributed; OR: Odds Ratio; CI: Confidence interval. Significant associations are shown in **bold.**

Table 2
genotypic association of HLA-G C1/C2 polymorphism in health controls and SARS-CoV-2 patients, showing codominant, dominant, recessive, over-dominant, and additive genetic models.

Genetic model type	Genotype/ variant	Controls		Covid-19 patients		Control vs Patients			
		Count	%	Count	%	OR (95 % CI)	P-value	AIC	χ^2
Codominant	**C2C2**	29	25.4	33	37.9	1			
	C1C2	44	38.6	37	42.5	0.74 (0.38–1.43)	**0.024**	264.1	6.1
	C1C1	41	36	17	19.5	**0.36 (0.17–0.77)**			
Dominant	**C2C2**	29	25.4	33	37.9	1	**0.0099**	262.4	4.47
	C1C2 + C1C1	85	74.6	54	62.1	**0.43 (0.22–0.83)**			
Recessive	**C2C2 + C1C2**	73	64	70	80.5	1	0.15	264.8	3.04
	C1C1	41	36	17	19.5	0.56 (0.31–1.02)			
Over-dominant	**C2C2 + C1C1**	70	61.4	50	57.5	1	0.57	266.4	2.04
	C1C2	44	38.6	37	42.5	0.71 (0.27–1.84)			
Log-additive	**–**	**–**	**–**	**–**	**–**	**0.61 (0.42–0.88)**	**0.0082**	262.6	–
Allotype model	**C1**		0.55		0.41	Ref			
	C2		0.45		0.59	**1.79 (1.20–2.67)**	**0.0047**	**–**	**7.69**

OR: Odds Ratio; CI: Confidence interval; AIC: Akaike information criterion. Significant associations are shown in **bold.**

Table 3
genotypic association of HLA-G 14 bp INS/DEL polymorphism in health controls and SARS-CoV-2 patients, showing codominant, dominant, recessive, over dominant, and additive genetic models.

Genetic model type	Genotype/ variant	Controls		Covid-19 patients		Control vs Patients			
		Count	%	Count	%	OR (95 % CI)	P-value	AIC	χ^2
Codominant	**ins/ins**	29	25.4	31	35.6	Ref			
	del/ins	56	49.1	38	43.7	0.43 (0.14–1.32)	0.33	266.7	1.99
	del/del	29	25.4	18	20.7	0.55 (0.14–2.07)			
Dominant	**ins/ins**	29	25.4	31	35.6	Ref	0.15	264.9	1.91
	del/ins + del/del	85	74.6	56	64.4	0.46 (0.16–1.34)			
Recessive	**ins/ins + del/ins**	85	74.6	69	79.3	Ref	0.95	266.9	0.38
	del/del	29	25.4	18	20.7	0.97 (0.33–2.87)			
Over-dominant	**ins/ins + del/del**	58	50.9	49	56.3	Ref	0.24	265.5	0.39
	del/ins	56	49.1	38	43.7	0.57 (0.23–1.45)			
Log-additive	**–**	**–**	**–**	**–**	**–**	0.73 (0.37–1.42)	0.35	266	–
Allele model	**del**		0.5		0.57	Ref			
	ins		0.5		0.43	0.74 (0.49–1.10)	0.15	–	1.92

OR: Odds Ratio; CI: Confidence interval; AIC: Akaike information criterion.

Table 4
Combinatory analysis of KIR/HLA ligand between COVID-19 patients and controls.

KIR/ligand	COVID-19 No. (%)	HEALTHY No. (%)	OR	CI 95 %	P
2DL2 + C1+	29.9	43.9	0.54	0.30–0.98	0.056
2DL2 + C1C1+	9.2	4.4	2.20	0.96–7.00	0.24
2DL2 + C1C2+	20.7	23.7	0.84	0.42–1.65	0.73
2DL3 + C1+	62.1	59.6	0.10	00.62–1.96	0.77
2DL3 + C1C1+	19.5	22.8	0.82	00.41–1.63	0.60
2DL3 + C1C2+	28.7	36.8	0.69	0.37–1.26	0.29
2DL1 + C2+	**80.5**	**66.7**	**2.058**	**1.06–3.97**	**0.037**
2DL1 + C2C2+	**42.5**	**26.3**	**0.44**	**0.23–0.82**	**0.013**
2DL1 + C1C2+	37.9	40.4	0.90	0.50–1.60	0.77
2DS2 + C1+	29.9	43	0.56	0.31–10.2	0.077
2DS2 + C1C1+	8.0	17.5	041	0.16–1.02	0.080
2DS2 + C1C2+	21.8	25.4	0.41	0.16–1.02	0.06
2DS1 + C2+	21.8	20.2	1.10	0.55–2.19	0.86
2DS1 + C2C2	10.3	7.0	1.52	0.56–4.14	0.45
2DS1 + C1C2	11.5	13.2	0.85	0.36–2.01	0.83

Significant associations are shown in **bold.**

SARS-Cov-2 (OR-0.36; P = 0.024). A negative relationship with the disease were observed in the dominant model C1C2 + C1C1 (OR = 0.43; P = 0.0099) and for the Log additive model (OR = 0.61; P = 0.0082). According to AIC, the dominant models could the best fitted one (AIC = 262.4). The allotype C2 was more frequent in patients than in control and could be associated with the bad outcome of the disease (OR = 1.79; P = 0.0047).

Concerning the 14 bp indel polymorphism in the 3′UTR of the HLA-G gene, no significant difference for any genotype was observed between the two groups for all the tested models (Table 3). Noting that for this polymorphism, the genotypes are in HWE (P > 0.05).

In order to study the prevalence of KIR gene in a context of their HLA-C1/C2 ligands, a combinatory analysis was performed considering both KIR receptor and ligand. Taking into account the specific ligand yet reported for some KIR receptors, 15 combinatory analyses for five KIR receptors (3 combination for each) were performed.

The frequency of KIR2DL1-HLA-C2 was significantly higher in patients with COVID-19 (80.5 % versus 66.7 %; P = 0.037; OR = 2.058). A slightly higher protective effect was observed for people sharing KIR2DL2 genes with homozygous C2C2 (Table 4).

4. Discussion and conclusion

The involvement of Killer Immunoglobulin-like Receptor (KIR) polymorphisms and the Human Immune response against viral infection has been reported by a significant number of researchers (Wang et al., 2018; Chaisri et al., 2019; van Erp et al., 2019).

The mechanism by which these NK cells react against SARS-CoV2 could be comparable to that reported against other common viruses. To achieve its antiviral action, NK cells involve extraordinarily diverse interactions between the family of KIR and MHC class I molecules (Vivier et al., 2008; Boyton and Altmann, 2007). HLA-A, -B, and -C molecules are the most important molecules which are reported to interact with KIR receptors. Additionally, they impact on the diversity and individualized human immune response between individuals (Wilson et al., 2000; González-Galarza Faviel et al., 2014).

In the present study, for the first time, the relationship between KIR genotypic polymorphism and their cognate ligand HLA-C1 and -C2 ligands with COVI-19 infection in Saudi Arabia has been reported. We did not find a strong association of KIR genes when considered each KIR gene, except for 2DL1 and 2DS4 which were significantly increased in patients with COVID-19. These results suggest that inhibitory 2DL1 and the activating 2DS4 might be associated with the outcome of patients with COVID-19. However,

this association should be retained take with great care because of the extended confidence interval range. Also, negative association between HLA-C1/C1 genotypes and COVID-19 were identified specially in codominant, dominant and Log additive models. This association should be taken with great care specially because of the slightly deviation from the HW equilibrium for this polymorphism. A large number of samples from other Saudi subpopulation should be considered later to confirm such association.

Conversely, a clear association was not identified between genotypes of the HLA-G 14 bp indel polymorphism and the explored disease.

Considering the interaction between some KIR receptors and their specific HLA-C allotype ligand, a significant positive association could be reported for the 2DL1 gene with its C2 ligand with infection. It is worth noting that 2DL1 was initially suspected to be positively associated with the infection. The associated was confirmed when considering its ligand at homozygote status. Overall, the study should be confirmed and consolidated with a use of a large and well-characterized cohort. This could facilitate the stratification of the patients and the identification of the effects of KIR in association with the clinical outcome of the SARS-CoV2 infected Saudi population.

In conclusion, KIR2DL1, and KIR2DS4, and the combination of 2DL1 + HLA-C2 + are associated with either susceptibility to be infected with SARS-CoV2 or protection in the Saudi population.

A full examination of the frequency, phenotype, and function of NK cells in COVI-19 patients is required in order to identify the precise mechanism of this association in the Saudi population.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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