Influence of *FcγRIIA* and *MBL* polymorphisms on severe acute respiratory syndrome

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Abstract

Polymorphisms of human Fc γ-receptor IIA (*FcγRIIA*) and mannose-binding lectin (*MBL*) genes have been associated with susceptibility to or severity of some infectious diseases. In order to investigate whether these genetic factors might influence susceptibility to infection with the severe acute respiratory syndrome-associated coronavirus (SARS-Cov) as well as the course and severity of the infection, we evaluated polymorphisms of *FcγRIIA* and *MBL* genes in DNA samples from a group of approximately 180 people from Hong Kong who were infected with SARS-Cov. These included 132 patients who had moderate course of SARS infection (home subgroup), 26 patients with a severe course requiring treatment in an intensive care ward (ICU subgroup) and a subgroup of 22 patients who died from SARS (deceased subgroup). A total of 200 normal blood donors from the same region were used as controls. A significant association was found between the FcγRIIA-R/R131 genotype and a severe course of SARS, with higher frequency of homozygosity for FcγRIIA-R/R131 in the ICU subgroup of SARS patients when compared with controls ($P = 0.03$; odds ratio: 3.2; 95% confidence interval: 1.1–9.1). In comparison with controls, a significant difference in linear trend distribution of FcγRIIA genotypes was seen among the severe SARS patients (ICU and deceased subgroups) without co-morbidity, and the incidence of FcγRIIA-H/H131 was lower in these patients as well. There were no significant differences in MBL genotypes and allele frequencies among SARS patients and controls. The study reveals that in addition to age and co-morbidity, *FcγRIIA* polymorphism of individuals may also influence outcome after infection with the SARS-Cov.

Severe acute respiratory syndrome (SARS), a new emerging infectious disease, originated in southern China in November 2002, was brought to Hong Kong in February 2003 and then spread to other countries during February to June 2003. Although the global cumulative total was more than 8000 cases with over 900 deaths, the majority of cases were from Southeast Asia. The causative agent of SARS is a novel coronavirus, the SARS-associated coronavirus (SARS-Cov). People of all ages were affected; however, health care workers were at high risk (1). Risk factors for death included old age and underlying illnesses, such as diabetes and cardiac disease (2, 3). It would be important to investigate whether host genetic factors could influence the susceptibility to SARS-Cov infection and its subsequent clinical course.

It is evident that host genetic factors are important in determining the susceptibility and outcome of infections caused by infectious pathogens, and the candidate gene

approach has been widely used to analyse possible association between genetic variations and human diseases with selection of genes based on *a priori* knowledge of disease pathogenesis and phenotypes. The human Fc γ-receptor IIA (*FcγRIIA*) is an important member of the Fc receptor family that plays a central role in the regulation of immunity and autoimmunity and the initiation of local inflammation. It forms an essential link between the humoral branch and the effector cells of the immune system. The *FcγRIIA* gene is known to contain a functional polymorphism with a *G→A* point mutation resulting in an arginine (R) or histidine (H) residue at amino acid position 131 in the Ig-like domain, and this polymorphism is known to affect receptor affinity and specificity. These polymorphisms have clinical implications and may represent a risk factor for certain diseases, either at the level of disease susceptibility or at the level of disease severity, including infectious diseases such as meningococcal disease, *Streptococcus pneumoniae* infections, dengue fever and the human immunodeficiency virus (HIV) infection (4–7).

Also, the innate immune system plays a role in limiting an infectious challenge in the early stages post exposure, during the lag time required to initiate long-lasting adaptive immunity. Mannose-binding lectin (MBL) plays a critical role in the first line of such host defence against pathogens via the lectin pathway of complement. MBL is able to bind microorganisms including bacteria, mycobacteria, certain parasites and viruses, such as the HIV, the respiratory syncytial virus, herpes virus and influenza virus (8). There are five single-nucleotide polymorphisms influencing serum MBL levels, which lead to several MBL-sufficient and MBL-deficient genotypes/haplotypes (9) including three single-nucleotide polymorphisms at codons 52 (Arg-Cys), 54 (Gly-Asp) and 57 (Gly-Glu) in exon 1 and two promoter polymorphisms at positions 550 (g–c, alleles H/L) and 221 (g–c, alleles X/Y) to form a number of coding genotypes and promoter haplotypes listed in Table 3. Polymorphisms in both *FcγRIIA* and *MBL* genes influence the inflammatory process and have a strong impact on susceptibility to numerous bacterial and viral infections. FcγRIIA-R131 and MBL coding mutations or deficient genotypes have been reported to be associated with susceptibility to infectious diseases (9–11). To examine the hypothesis that polymorphisms of *FcγRIIA* and *MBL* genes in SARS patients are genetic factors influencing susceptibility to the infection and severity of the disease post infection, we studied polymorphisms of *FcγIIRA* and *MBL* genes in DNA samples from a group of 180 Hong Kong SARS patients with different clinical outcomes and compared these with 200 normal blood donors from the same region as a control group.

Materials and methods

We studied a total of 180 unrelated patients who were diagnosed as having SARS both clinically and serologically in the Prince of Wales hospital in Hong Kong, including (i) home subgroup: 132 SARS patients with moderate SARS who had recovered without the need for ventilation or intensive care; (ii) ICU subgroup: 26 patients with severe course of SARS who required ventilation and/or intensive care and (iii) deceased subgroup: 22 patients who died from SARS. Patients' demographics are summarized in Table 1. The control group consisted of 200 blood donors from Hong Kong. The study was approved by the Institutional Human Ethics committees of the Prince of Wales Hospital and the Hong Kong Red Cross Blood Transfusion Service. DNA was extracted from patients' blood samples using the QIAamp DNA mini kit (Qiagen, Hilden, Germany). DNA was extracted from blood samples of blood donors using a standard salting-out

Table 1 Patient demographics (subgroups)

	Home subgroup ($n = 132$) (%)	ICU subgroup ($n = 27$) (%)	Deceased subgroup ($n = 21$) (%)
Mean age[a]			
≥70 years	5 (4)	0	10 (48)
<70 years	127 (96)	27 (100)	11 (52)
Gender			
Male	56 (42)	16 (59)	13 (62)
Female	76 (58)	11 (41)	8 (38)
Race			
Chinese	132 (100)	27 (100)	21 (100)
Underlying illness			
(Diabetes, hypertension and others)	25 (19)	9 (33)	8 (38)

CI, confidence interval; OR, odds ratio.

[a]In comparison with either home or ICU subgroup, among deceased subgroup patients the incidence of patients who are ≥70 years is significantly higher: $P < 0.0001$; OR = 32 (95% CI, 10–101) or OR = 33 (95% CI, 6–186), respectively.

procedure (12). Other control groups were Australian blood donors whose FcγRIIA or MBL genotypes have been reported in separate studies (5, 13). For FcγRIIA genotyping, sequence-specific polymerase chain reaction (SSP) was used to identify the FcγRIIA-R-H-131 polymorphisms as described previously (7). For MBL2 genotyping, the 550 (H/L), the 221 (X/Y) and codon 52Cys, 54Asp, and 57Glu MBL2 polymorphisms were determined in the patients and controls, using the SSP method as described previously (14). Data were analysed for differences in distribution of FcγRIIA genotypes among groups using χ^2-test for linear trend or independence (2×3 contingency tables and χ^2-analysis). Frequencies of MBL genotype and FcγRIIA genotype (e.g. FcγRIIA-R/R131 *vs* combined FcγRIIA-R/H131 and FcγRIIA-H/H131 or FcγRIIA-H/H131 *vs* combined FcγRIIA-R/H131 and FcγRIIA-R/R131) as well as the allele frequencies were compared among groups using Fisher's exact test (2×2 contingency tables, two-sided or one-sided as indicated). Differences were considered significant when $P < 0.05$.

Results

FcγIIRA polymorphisms

The distribution of FcγRIIA genotypes and allele frequencies among the subgroups of SARS patients and controls were evaluated and are summarized in Table 2. There were no statistically significant differences in FcγRIIA genotypes (R/R, R/H and H/H) between the whole SARS patient group and the controls (12, 45 and 43 *vs* 9, 42 and 49%, respectively). When analysing the SARS subgroups separately, ICU patients with severe outcome of SARS had a significant increase of R/R genotype compared with the controls (23 *vs* 9%, two-sided $P = 0.03$). To eliminate the influence of other known risk factor such as co-morbidity, we also evaluated the distributions of FcγRIIA genotypes among the SARS patients without underlying illness. Difference in linear trend distribution of the genotypes (R/R, R/H and H/H) was significant between the overall SARS patients without underlying illness and the normal controls (14, 47 and 39 *vs* 9, 42 and 49%, respectively; $P = 0.0419$) and between the severe SARS subgroup (ICU plus deceased subgroups) without underlying diseases and the controls (20, 50 and 30 *vs* 9, 42 and 49%, respectively; $P = 0.0178$), but a similar distribution of the genotypes among Home subgroup without underlying illness and the controls (12, 46 and 42 *vs* 9, 42 and 49%, respectively; $P = 0.1764$) was observed. A significant low H/H was observed among the severe SARS subgroup (ICU plus deceased subgroups) without underlying diseases compared with the controls (30 *vs* 39%, one-sided $P = 0.0388$). In comparison with the patients in home, ICU and deceased subgroups, distribution of the genotypes (R/R, R/H and H/H) among these patients without underlying illness was 12, 46 and 42 *vs* 10, 45 and 45%; 24, 47 and 29 *vs* 23, 38 and 38%; and 15, 54 and 31 *vs* 9, 48 and 43%, respectively (Table 2). There was variation at the allele frequency level with the ICU patients having an increased FcγRIIA-R131 frequency and reduced FcγRIIA-H131 but not statistically significant compared

Table 2 Distribution of FcγRIIA genotypes in subgroups of Hong Kong patients with severe acute respiratory syndrome (SARS) and control group of Hong Kong blood donors

	Genotype, *n* (%)[a]				Allele frequency	
Controls and group or subgroup of patients	R/R	R/H	H/H	*P*-value; Odds ratio (95% CI) (2×2 contingency tables)	R131	H131
Controls, Hong Kong blood donors ($n = 200$)	17 (9)	85 (42)	98 (49)		0.30	0.70
All patients with SARS ($n = 179$)	21 (12)	80 (45)	78 (43)	In comparison with controls: 0.31; 1.4(0.7–2.8)	0.34	0.66
Without underlying illness *(n = 137)*	19 (14)	64 (47)	54 (39)		0.37	0.63
Home ($n = 132$)	13 (10)	60 (45)	59 (45)	In comparison with controls: 0.7; 1.2 (0.6–2.5)	0.33	0.67
Without underlying illness *(n = 107)*	13 (12)	49 (46)	45 (42)		0.35	0.65
Deceased ($n = 21$)	2 (9)	10 (48)	9 (43)	In comparison with controls: 1.0; 1.1 (0.2–5)	0.33	0.67
Without underlying illness *(n = 13)*	2 (15)	7 (54)	4 (31)		0.42	0.58
ICU ($n = 26$)	6 (23)	10 (38)	10 (38)	In comparison with controls: 0.03; 3.2 (1.1–9.1); in comparison with home group: 0.09; 2.7 (0.9–8)	0.42	0.58
Without underlying illness (n = 17)	4 (24)	8 (47)	5 (29)		0.47	0.53

CI, confidence interval.

[a]In comparison with control group of Hong Kong blood donors, frequencies of FcγRIIA-R/R131 *vs* non-FcγRIIA-R/R131 among patients with severe SARS (ICU) showed statistically significant differences (2×2 contingency table; two-sided $P = 0.03$; OR: 3.2, 95% CI: 1.1–9.1) and frequencies of FcγRIIA-H/H131 *vs* non-FcγRIIA-H/H131 among patients with the severe SARS group without underlying illness ($n = 30$, ICU and deceased subgroups) reached statistically significant differences (2×2 contingency table; one-sided $P = 0.0388$; OR: 0.446, 95% CI: 0.19–1.02). Difference in linear tread distribution of genotypes (R/R, R/H and H/H) between the overall SARS patients without underlying diseases and controls was significant (2×3 contingency table; $P = 0.0419$), and between the severe SARS group without underlying illness ($n = 30$, ICU and deceased subgroups) and controls was also significant (2×3 contingency table; $P = 0.0178$).

with the controls and home subgroup of SARS patients (0.42 *vs* 0.3 and 0.33; 0.58 *vs* 0.70 and 0.67, respectively).

MBL polymorphisms

No significant differences in MBL genotypes and allele frequencies were observed among the subgroups of SARS patients and the controls as summarized in Table 3. Interestingly, the frequency of 54Asp allele was elevated in the home subgroup (0.22 *vs* 0.12 and 0.15, respectively) with 4% of 54-Asp/Asp homozygotes compared with ICU/deceased subgroups and the controls, resulting in slightly higher deficient genotypes of MBL in home subgroup. Apparently, 54Asp is a predominant variant in Chinese populations (both controls and patients), while only one out of 200 Hong Kong blood donors carries the 52Cys variant. SARS patients who died had a high level of HYA/HYA plus HYA/LYA promoter haplotypes compared with home and ICU groups, and the controls (40 *vs* 26, 28 and 30%, respectively), but these differences were not statistically significant.

Table 3 Comparison of mannose-binding lectin (MBL) allele and haplotype frequencies between the patients with severe acute respiratory syndrome (SARS) and blood donors in Hong Kong

		Number of subgroup of patients with SARS (%)		
Allele/genotype/haplotype	Number of Hong Kong blood donors (%) $n = 200$	Home, $n = 130$	ICU, $n = 26$	Deceased $n = 20$
Coding genotypes				
A/A	139 (70)	81 (62)	19 (76)	15 (75)
A/O				
A/52Cys	1	0	0	0
A/54Asp	60 (30)	44 (34)	6 (24)	5 (25)
A/57Glu	0	0	0	0
O/O				
52Cys/52Cys	0	0	0	0
54Asp/54Asp	0	5 (4)	0	0
54As/52Cys	0	0	0	0
54Asp/57Glu	0	0	0	0
Promoter genotypes				
−550 alleles (H/L)				
H/H	27 (14)	21 (16)	5 (20)	4 (20)
H/L	111 (56)	65 (50)	11 (44)	10 (50)
L/L	62 (31)	44 (34)	9 (36)	6 (30)
−221 alleles (X/Y)				
X/X	9 (4)	4 (3)	1 (4)	2 (10)
X/Y	72 (36)	45 (35)	9 (36)	5 (25)
Y/Y	119 (60)	81 (62)	15 (60)	13 (65)
Promoter haplotypes				
HYA/HYA	27 (14)	20 (15)	5 (20)	4 (20)
HYA/LYA	32 (16)	15 (11)	2 (8)	4 (20)
HYA/LXA	39 (20)	28 (22)	5 (20)	2 (10)
LYA/LYA	12 (6)	5 (4)	3 (12)	0
LYA/LXA	20 (10)	9 (7)	3 (12)	3 (15)
LXA/LXA	9 (4)	4 (3)	1 (4)	2 (10)
HYA/O	39 (20)	23 (18)	4 (16)	4 (15)
LYA/O	8 (4)	12 (9)	1 (4)	1 (5)
LXA/O	13 (6)	9 (7)	1 (4)	0
Sufficient (HYA/A, LYA/A, HYA/O and LYA/O)	178 (89)	112 (86)	23 (92)	18 (90)
Deficient (O/O, LXA/O and LXA/LXA)	22 (11)	18 (14)	2 (8)	2 (10)
MBL54 genotype/allele				
54-Gly/Gly	140 (70)	81 (62)	19 (76)	15 (75)
54-Gly/Asp	60 (30)	44 (34)	6 (24)	5 (25)
54-Asp/Asp	0	5 (4)	0	0
Gly54	0.85	0.78	0.88	0.88
Asp54	0.15	0.22	0.12	0.12

Discussion

Study of the role of host gene polymorphisms in human diseases, especially how these polymorphisms influence both the susceptibility to diseases and the course of disease development, has been an important area of investigation. Unlike many other genes where genetic variants have no clear functional contribution to a population disease profile, the FcγRIIA exhibits a clear functional difference between R131 and H131 allotypes and has relevance for some infectious and autoimmune diseases. The results of this study demonstrate for the first time that FcγRIIA-R/R131 genotype was significantly associated with severity of SARS infection ($P < 0.05$). Patient's age is an important prognostic factor influencing survival post SARS infection, because almost half of the deceased, compared to only five out of 159 patients who recovered (home and ICU subgroups), were aged over 70 years (Table 1). However, in both home and ICU patient subgroups in which the majorities were of a younger age group, *FcγRIIA* polymorphisms appear to influence the course of SARS infection. Co-morbidity might have influenced severity of SARS infection, but *FcγRIIA* polymorphisms was still significant as distribution of FcγRIIA genotypes was different among the severe SARS patients (when the ICU and deceased patients were amalgamated) after corrections for co-morbidity, compared with the controls ($P < 0.05$). Furthermore, patients without co-morbidity from both ICU and deceased subgroups displayed a lower frequency of the FcγRIIA-H/H131 genotype. Our results suggest that R/R could be a risk factor for developing a more severe course of SARS-Cov infection while H/H might have a protective role in the outcome of SARS infection.

Interestingly, during the SARS outbreak, plasma from convalescent patients who recovered from the SARS infection was used to treat some cases of SARS patients with favourable responses (15, 16). Studies on viral neutralizing activity of anti-SARS plasma have been reported (17, 18), but the functional relevance of antibody against SARS and whether this antibody might work via a Fc-dependent receptor remain to be established. Because activation of FcγRIIA is initiated by antibody binding followed by multiple biologic processes such as signal transduction, phagocytosis and antibody-dependent cellular cytotoxicity, release of inflammatory mediators, and interaction with other Fc receptors and complement factors, it would be useful to study the FcγRIIA genotypes in parallel with the presence/level of antibody to SARS-Cov in these SARS patients. Additionally, FcγRIIA genotyping carried out on patients may help to predict the efficacy of antibody-based immunotherapy in the future.

FcγRIIA genotypes also exhibit ethnic variation with a low R/R and a high H/H frequencies in some Asian populations compared with Caucasians and Africans (19). Distribution of FcγRIIA genotypes in Hong Kong blood donors is similar to that among other Asian populations, including Chinese, Vietnamese and Japanese. Ethnic variation of FcγRIIA genotypes may explain why certain infections vary among different ethnic populations; however, this needs to be studied further.

In a recent study, Ip et al. looked at *MBL* polymorphisms and levels of *MBL* in 569 patients with SARS from Hong Kong and showed that there was a significant association between low/deficient levels or haplotypes of MBL and susceptibility to SARS-Cov infection (20). Interestingly, MBL genotype profiles are similar between our patients and the Ip group. However, no statistically significant differences between SARS patient groups and controls were observed for the MBL genotypes in our study, despite a higher 54Asp allele frequency found in home subgroup compared with controls or ICU/deceased subgroups. The smaller size of our study group could be the reason why our study did not demonstrate any significant differences in MBL genotypes/haplotypes and susceptibility to SARS-Cov. In comparisons of *MBL* polymorphisms between Hong Kong blood donors and

Table 4 Comparison of mannose-binding lectin (MBL)-54 allele frequencies and genotypes in Hong Kong blood donors with other ethnic groups

	Hong Kong blood donors, $n = 200$ (%)	Australian blood donors, $n = 236$ (%) (13)	Vietnamese $n = 264$ (%) (6)
MBL genotypes[a]			
Sufficient (HYA/A, LYA/A, HYA/O and LYA/O)	178 (89)	190 (81)	Unknown
Deficient (O/O, LXA/O and LXA/LXA)	22 (11)	46 (19)	Unknown
MBL54 genotype/allele			
54-G/G	140 (70)	173 (73)	202 (76.5)
54-G/Asp	60 (30)	58 (25)	58 (22)
54-Asp/Asp	0	5 (2)	4 (1.5)
G54	0.85	0.86	0.875
Asp54	0.15	0.14	0.125

[a]In comparison with Australian blood donors, frequencies of deficient MBL genotypes *vs* sufficient MBL genotypes among Hong Kong blood donors showed statistically significant differences ($P = 0.017$).

Australian blood donors and healthy Vietnamese children, 54Asp seems to be a predominant variant in the Chinese population with only one out of 200 (0.5%) Hong Kong blood donors carrying the 52Cys variant (Table 3), while 42% of Australian blood donors carry either the 54Asp or/and the 52Cys, 57Glu variants (13). However, less deficient and more sufficient MBL genotypes were found in Hong Kong blood donors than those in Australian blood donors ($P < 0.05$), while MBL-54 allele frequencies and genotypes in Hong Kong blood donors were similar to those among the Australian blood donors and Vietnamese (Table 4).

In summary, our data are in line with previous reports that age and existing medical co-morbidity play a major role in determining the mortality and morbidity of SARS-Cov infection. In addition, the major finding of our study is a significant association between FcγRIIA-R/R genotype and the severity of SARS-Cov infection. Further studies are required to explore the possible role of these and other host genetic factors that may influence the susceptibility and disease outcome of SARS-Cov infection.

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