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ORIGINAL ARTICLE

Candidate Genes Associated with Susceptibility for SARS-Coronavirus

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Abstract Assuming that no human had any previously acquired immunoprotection against severe acute respiratory syndrome coronavirus (SARS-CoV) during the 2003 SARS outbreak, the biological bases for possible difference in individual susceptibility are intriguing. However, this issue has never been fully elucidated. Based on the premise that SARS patients belonging to a given genotype group having a significantly higher SARS infection rate than others would imply that genotype group being more susceptible, we make use of a compartmental model describing disease transmission dynamics and clinical and gene data of 100 laboratory confirmed SARS patients from Chinese Han population in Taiwan to estimate the infection rates of distinct candidate genotype groups among these SARS-infected individuals. The results show that CXCL10(−938AA) is always protective whenever it appears, but appears rarely and only jointly with either Fgl2(+158T/*) or HO-1(−497A/*), while (Fgl2)(+158T/*) is associated with higher susceptibility unless combined with CXCL10/IP-10(−938AA), when jointly is associated with lower susceptibility. The novel modeling approach proposed, which does not require sizable case and control gene datasets, could have important future public health implications in swiftly identifying potential high-risk groups associated with being highly susceptible to a particular infectious disease.

Keywords SARS · Genotype · Susceptibility · Compartmental model · Transmission dynamics

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1. Introduction

The power of genotype-phenotype association studies are often weakened by the limited number of patients in the cohort studied. This is particularly true in the cases of emerging infectious diseases, e.g., severe acute respiratory syndrome (SARS), a new infectious disease caused by a novel coronavirus (SARS-CoV) that carries a significant mortality rate (Peiris et al., 2003; Tsui et al., 2003). Possible association of various polymorphisms of human genes has been reported in several studies (Lin et al., 2003; Ng et al., 2004; Sui et al., 2004; Ip et al., 2005; Zhang et al., 2005; Yuan et al., 2005; Chen et al., 2006a, 2006b; Chong et al., 2006; He et al., 2006). Moreover, it has been observed that some people were infected while others in the same environments were free from infection, suggesting a possible role of host genetic factors in susceptibility to SARS-CoV infection (Lee, 2003). However, in all of these association studies, statistical association analysis was employed where inadequate sample size sometimes weakens the results.

In a recent genetic study on SARS patients focusing on single nucleotide polymorphisms (SNPs) associated with nasopharyngeal shedding of SARS-CoV (Chen et al., 2006a, 2006b), the authors genotyped 282 SNPs of 64 genes and identified 4 SNPs that are associated with level of nasopharyngeal virus shedding of SARS-CoV including one SNP on the fibrinogen-like protein 2 (FGL2) at amino acid position 53 (Fgl2 G53E). In a subsequent work (Ho et al., 2008), the genotyping data were further analyzed along with the duration of clinical illness (number of days between onset of illness and hospital discharge) which found that severity of SARS infection was significantly associated with differences in genotype distribution of three genes: fibrinogen-like protein (Fgl2) at C+158T downstream to the start codon that results in a nonsynonemous amino acid substitution from glycine to glutamic acid at amino acid G53E being a dominant risk variant; CXCL10/IP-10 at G−938A upstream to the start codon with −938A being a risk and −938G being a protective variant; and heme oxygenase 1 (HO-1) at T−497A with −497A being a dominant risk variant.

In light of the possible connection between susceptibility and severity, we employed a compartmental mathematical model which describes the disease transmission dynamics and statistical parameter estimation, namely, three-stage least squares (3SLS) parameter estimation procedure (Hsieh et al., 2004, 2007), to estimate the infection rates of different genotype groups of infectees in order to further explore the question of whether FGL2(+158T/*), alone or in combination with CXCL10(−938AA) or HO-1(−497A/*), could be associated with susceptibility of individuals to SARS-CoV infection.

2. Data

For our study, the genotype data comes from 100 Chinese Han patients out of 480 confirmed SARS cases in Taiwan, which includes 346 cases officially confirmed by Taiwan Center for Disease Control (TCDC) during the outbreak in 2003 and 134 additional cases identified from a subsequent TCDC-sponsored large-scale seroepidemiological follow-up study to search for previously undiscovered SARS cases (Hsieh et al., 2005). Genotyping of 281 loci of single nucleotide polymorphism (SNPs) located on 65 candidate genes was performed for these cases. Some genotyped cases were deleted for this study due to

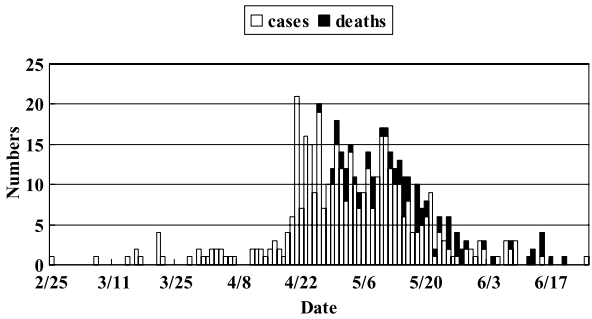

Fig. 1 Daily incidence of 461 confirmed SARS cases in Taiwan by onset date and incidence of deaths by date of death, 2/25–6/25, 2003. (Source: Taiwan CDC and Hsieh et al., 2007.)

the lack of clinical data, others were omitted so that there are no kinship (parent-child or siblings) among the cases so there is no blood relation among the cases, although there are two couples. The resulting data set is that of 100 cases we will study. Of these 100 patients genotyped, five had died of SARS and the rest had recovered and discharged from hospital. The genotype frequencies of the 100 cases with their clinical severity are given in Table A.1 of the Appendix. Note that genotype data for all 480 confirmed SARS cases in Taiwan is not available due to difficulty in collecting samples, since 85 of the confirmed SARS cases had died and many other who had recovered did not give consent for genotyping. This limitation led to difficulty in carrying out reliable statistical association study for gene susceptibility to SARS, which motivates our present modeling study.

In order to make use of the case data for the estimation of the infection rates of different genotype groups with our model, precise clinical history of each case is needed to fit the model. Subsequently, 19 cases whose clinical history had not been fully documented were removed from our data set, and hence the estimation is carried out with the case data of 461 confirmed SARS cases, including 336 TCDC confirmed cases and 125 additional laboratory confirmed cases (see Fig. 1 for daily incidence data of these 461 cases).

3. Compartmental model

We focus our study on addressing the question of whether the risk genotype for clinical severity is associated with susceptibility to SARS. In order to do so, we make use of a discrete-time compartmental model (Hsieh et al., 2004), to estimate the infection rate of different genotype groups. The model used in this work is traditionally used to describe transmission dynamics of infectious diseases (Anderson and May, 1991). Similar modeling approach has been used to estimate the different infection rates of HIV-infected individuals during different stages of illness (Rapatski et al., 2005). We carried out the model parameter estimation in such a way so that we do not need to distinguish the hospitalized patients by their clinical severity, nor do we make the distinction between infections by infectives of different genotypes. Instead, we only distinguish the infected cases by their genotype, thus address the question of whether their genotype played in part in their chance of being infected. A typical model flowchart with three genotype combinations is given in Fig. 2 (the subscript "n" in the model equations, denoting the time unit, was

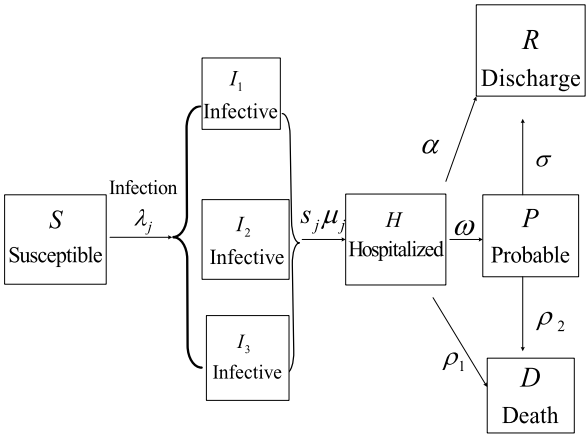

Fig. 2 Model dynamics with infective (I) cases divided by three genotype combinations.

deleted for brevity). Note that from Table A.1, three are three genotype combinations of Fgl2(+158T/*) and HO-1(−497A/*), but only two combinations for CXCL10(−938AA).

The variables are the Susceptibles (S_n), those who had not infective at time n; Infectives ($I_{j,n}$) of genotype combination j and are infective at time n; Hospitalized cases (H_n) who are diagnosed and hospitalized by time n; Probable cases (P_n), those who have been confirmed to be probable SARS cases (see, e.g., Hsieh et al., 2004); Discharged cases (R_n) who have recovered by time n; and Deceased (D_n) who have died by time n. The time unit is in days.

The discrete time model equations, where the numbers of individuals in each stage (or compartment) of disease progression on day $n+1$ are given as functions of the numbers of individuals in various stages of disease progression on day n, are as follows:

$$I_{j,n+1} = I_{j,n} + \lambda_{j,n} - \mu_j I_{j,n}, \quad \text{where } j = 1, 2, \ldots, m,$$

$$H_{n+1} = H_n + \sum_{j=1}^{m} s_j \mu_j I_{j,n} - (\omega + \alpha + \rho_1) H_n,$$

$$P_{n+1} = P_n + \omega H_n - (\sigma + \rho_2) P_n,$$

$$R_{n+1} = R_n + \sigma P_n + \alpha H_n,$$

$$D_{n+1} = \rho_2 P_n + \rho_1 H_n.$$

The disease incidence $\lambda_{j,n}$ of individuals of genotype combination j on day n is given by

$$\lambda_{j,n} = s_j \lambda_n = \beta_j I_n + \gamma_j H_n, \quad \text{where } I_n = \sum_{j=1}^{m} I_{j,n} \text{ and } m = 2 \text{ or } 3.$$

The model parameters as listed below:

$\lambda_{j,n}$—the incidence of SARS cases with genotype combination j on day n.
λ_n—the incidence of SARS cases on day n.
β_j—the infection rate of new cases with genotype combination j infected by an infective (I_n) on day n.
γ_j—the infection rate of new cases with genotype combination j infected by a hospitalized infective (H_n) on day n.
s_k—the genotype frequency of the kth genotype combination.
μ_j—the hospitalization rate out of $I_{j,n}$ compartment.
ω, α, and ρ_1—the transfer rate out of H_n and into P_n, R_n, and D_n, respectively.
σ and ρ_2—the transfer rate out of P_n and into R_n and D_n, respectively.

During SARS outbreak, those suspected of SARS were hospitalized, sometimes without full isolation. A reclassification procedure allowed those who were laboratory confirmed to have been infected by SARS to be reclassified as probable case, and receive full isolation (Hsieh et al., 2005). Hence, we assume infections occurred only due to the infectives ($I_{j,n}$) and hospitalized cases (H_n). We also assume homogeneous mixing so individuals of all genotypes have the same opportunity of getting infected.

In order to distinguish the difference in infection among the distinct genotype groups, we divide only the infected classes (I) into genotype combinations characterized by the presence of each of the three genotypes, namely, fibrinogen-like protein (Fgl2)(+158T/*), CXCL10/IP-10(−938), and heme oxygenase 1 (HO-1)(−497A/*), using the model described. For example, in the model used for (Fgl2)(+158T/*), the group I_1 for those with (Fgl2)(+158T/*) only is denoted by (+ − −) in the tables hereafter, I_2 for those with (Fgl2)(+158T/*) combined with other genotypes is denoted by (+ * *), and I_3 for those without this genotype is denoted by (− * *). All other groups (as shown in Table A.1 of Appendix) are denoted likewise. We also obtain estimates of the onset-to-hospitalization time for each genotype group directly from the clinical case history of the 100 patients in our genotype data (Table 2). Note that the second gene, CXCCL10/IP-10(−938AA), only appears jointly with the risk genotypes of either of the other two genes, hence there are only two groups to compare. By only distinguishing the genotype difference in the infective class ($I_{j,n}$), our basic hypothesis is that assuming everything else being equal, the genotype group with the relatively higher infection rate must be more susceptible to SARS. In other words, we only identify the infection rate by the genotype of the infectee but not the infector, since our goal is to study gene association with susceptibility.

The model construction is similar to Hsieh et al. (2004), except with separate compartments $I_{k,n}$ are assigned to infectives of different genotype combinations, with $k = 1, 2$, or 3, denoting the kth genotype combination group of the particular gene to be studied. The model contains a daily incidence $\lambda_{j,n}$ of SARS cases of the jth genotype. We assume the daily incidence of each genotype group is, on the average, in the same proportion as its genotype frequency s_j. Hence, we have $\lambda_{j,n} = s_j \lambda_n$ where λ_n is the daily incidence of all SARS cases.

The genotype frequencies s_j are as given in Table A.1 of the Appendix. For the transfer rate or hospitalization rate μ_j from the jth infective class ($I_{j,n}$) into the hospitalized class (H_n), we compute the mean onset-to-hospitalization time from $I_{j,n}$ compartment into the hospitalized class, also given in Table A.2 of the Appendix, and take the reciprocal fraction to be the respective transfer rate. For the estimation, we assume that the 461 case data used have the same genotype frequency s_j and transfer rate μ_j as the 100 case genotype data. All other parameters are to be estimated.

4. Estimation procedure

To estimate the model parameters from the data, the three-stage least squares method (3SLS) commonly used in econometrics (Pindyck and Rubinfeld, 1998) is utilized which involves the application of generalized least squares estimation to a system of equations. We treat a linear system of equations as a multiequation simulation model, which allows us to account for the interrelationship within a set of variables, namely, $I_{k,n}$ and H_n with $k = 1$, 2, and 3, which are called endogenous variables. This procedure has previously been used also for estimation of model parameters in Hsieh et al. (2004, 2007), where a detailed description of the estimation procedure can be found. Note that the reclassification rate from H_n to P_n, ω, was obtained by letting $\omega = 1/7.5 = 0.132$, since the mean reclassification time was computed to be 7.5 days in Hsieh et al. (2005).

5. Results

We estimate the infection rate β_j of each of the jth genotype combination groups of infected individuals by an infective of unspecified genotype. The results show that, for all three genes, the infection rate γ_j by hospitalized class (H_n) are not significantly different from 0. However, the infection rate, denoted by β, is different for each genotype combination group of infectives. The results of the estimation of the infection rates with confidence intervals (CI) are given in Table 1 and graphically in Fig. 3. The estimates for the parameters α, ρ_1, σ, and ρ_2 for each genotype combination are omitted for sake of brevity.

From our results, Fgl2(+158T/*) clearly is a risk genotype for infection since we have $\beta = 0.4432$ (95% CI: 0.4060–0.4804) for those with this genotype only, as compared to $\beta = 0.4038$ (95% CI: 0.3833–0.4244) for those with this genotype in combination with the genotype of at least one of the other two genes in question, and to $\beta = 0.3204$ (95% CI: 0.2825–0.3582) for those without this genotype. The difference in infection rate between those with Fgl2(+158T/*) only and those with this genotype in combination with the genotype of at least one of the other two genes is statistically significant.

Table 1 Parameter estimates for infection rate β of genotype combinations grouped by Fgl2(+158T/*), CXCCL10/IP-10(−938AA), and HO-1(−497A/*). For example, (+ − −) denotes presence of this risk genotype only, (− * *) denotes absence of this risk genotype, and (+ * *) are all others. All p-values are $< .0001$

Genotype	Estimates for infection rate β	95% CI
Fgl2(+158T/*)		
(+ − −)	0.4432	(0.4060, 0.4804)
(+ * *)	0.4038	(0.3833, 0.4244)
(− * *)	0.3204	(0.2825, 0.3582)
CXCCL10/IP-10(−938AA)		
(* + *)	0.2558	(0.2186, 0.2929)
(* − *)	0.3745	(0.3369, 0.4121)
HO-1(−497A/*)		
(− − +)	0.3274	(0.2900, 0.3648)
(* * +)	0.3808	(0.3432, 0.4183)
(* * −)	0.3674	(0.3447, 0.3901)

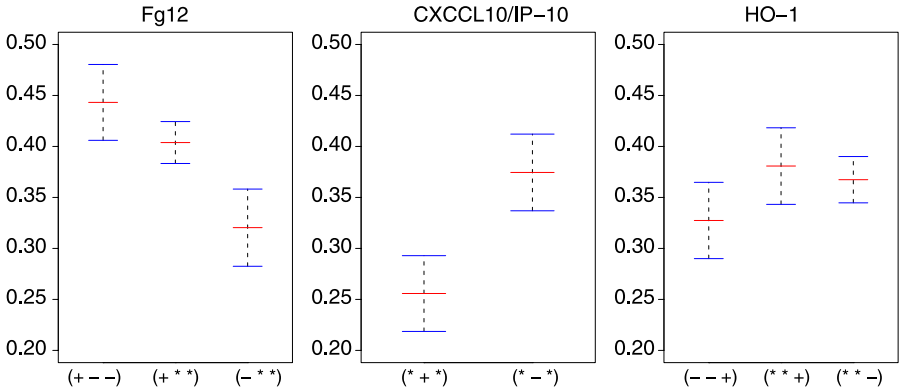

Fig. 3 Graphs for estimates of infection rate β of genotype combinations grouped by Fgl2(+158T/*), CXCCL10/IP-10(−938AA), and HO-1(−497A/*) in Table 1. For each case, red segment denotes the mean estimate with blue segments indicating the 95% CI of the estimate.

CXCL10(−938AA) is a protective genotype where we have $\beta = 0.2558$ (95% CI: 0.2186–0.2929) for those with this genotype compared to $\beta = 0.3745$ (95% CI: 0.3369–0.4121) for those without this genotype, since the difference in infection rate is statistically significant. The role of HO-1(−497A/*) is inconclusive due to overlapping confidence intervals, since we have $\beta = 0.3274$ (95% CI: 0.2900–0.3648) for those with this genotype only, as compared to $\beta = 0.3808$ (95% CI: 0.3432–0.4183) for those with this genotype in combination with the genotype of at least one of the other two genes, and to $\beta = 0.3674$ (95% CI: 0.3447–0.3901) for those without this genotype. It follows that there must be some complicated joint effect of the genotypes at work. Moreover, the association between HO-1(−497A/*) and SARS susceptibility is less significant when compared with that of the other two genotypes.

In order to further study possible joint effects of these risk or protective genotypes, we divided the infective class into two genotype combination groups—one with at least two of the three genotypes and the other without. The results of parameter estimation are given in Table 2 and graphically in Fig. 4.

The results show that genotype combination of CXCL10(−938AA) and HO-1(−497A/*) is also protective with $\beta = 0.2763$(95% CI: 0.2391–0.3114) for those with this genotype combination as compared to $\beta = 0.3691$ (95% CI: 0.3315–0.4067) for those without. However, the genotype combination of Fgl2(+158T/*) and CXCCL10/IP-10(−938AA) is protective with $\beta = 0.2839$ (95% CI: 0.2467–0.3210) for those with this genotype combination compared to $\beta = 0.3615$ (95% CI: 0.3239–0.3990) for those without, even though Fgl2(+158T/*) was a risk genotype by itself. Moreover, the genotypes combination of Fgl2(+158T/*) and HO-1(−497A/*) is a risk genotype combination for SARS with $\beta = 0.4308$ (95% CI: 0.3937–0.4680) for those with that genotype combination compared to $\beta = 0.3270$ (95% CI: 0.2892–0.3647) for those without.

It is interesting to know that CXCL10(−938AA) occurred in only 13 of the 100 cases in our data, and only in combination with one genotype of at least one of the other two genes. However, it appears to be protective whenever it is present, in any combination with other genes. The results offer strong proof regarding gene association of Fgl2(+158T/*)

Table 2 Parameter estimates for infection rate β of the genotype combinations grouped by presence of any two of the three genotypes, Fgl2(+158T/*), CXCCL10/IP-10(−938AA), and HO-1(−497A/*). (+ + *) denotes presence of both genotypes, (* * *) denotes all others. The p-values are $< .0001$

Genotype	Estimates for infection rate β	95% CI
CXCCL10/IP-10(−938AA) and Fgl2(+158T/*)		
(+ + *)	0.2839	(0.2467, 0.3210)
(* * *)	0.3615	(0.3239, 0.3990)
Fgl2(+158T/*) and HO-1(−497A/*)		
(+ * +)	0.4308	(0.3937, 0.4680)
(* * *)	0.3270	(0.2892, 0.3647)
CXCCL10/IP-10(−938AA) and HO-1(−497A/*)		
(* + +)	0.2763	(0.2391, 0.3134)
(* * *)	0.3691	(0.3315, 0.4067)

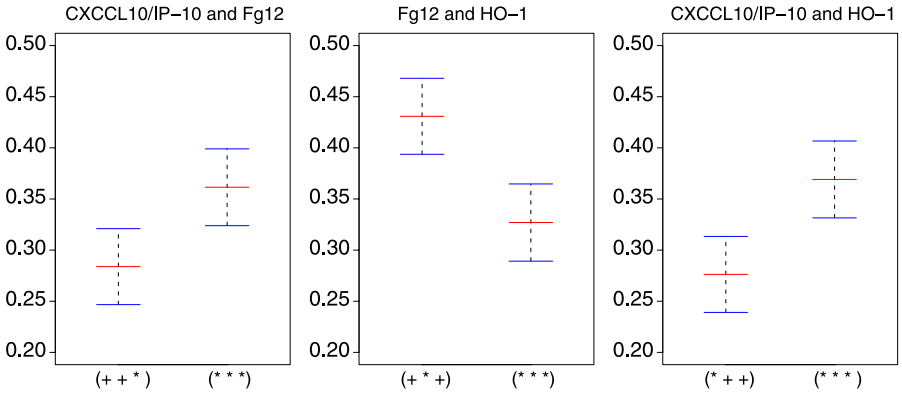

Fig. 4 Graphs for estimates of infection rate β of the genotype combinations grouped by presence of any two of the three genotypes, Fgl2(+158T/*), CXCCL10/IP-10(−938AA), and HO-1(−497A/*) in Table 2. For each case, red segment denotes the mean estimate with blue segments indicating the 95% CI of the estimate.

and CXCCL10/IP-10(−938AA) to SARS-CoV. The result for HO-1(−497A/*) is less clear, indicating the need for further study.

6. Conclusions and discussions

For this study, clinical data of 461 SARS patients were used in the parameter estimation, while 100 cases of this group of 461 had genetic data which was used to compute gene frequencies for the model. To summarize our results in words, Fgl2(+158T/*) is a risk variant, unless combined with CXCL10(−938AA) genotype. CXCL10(−938AA) assumes a protective role whenever it appears, but it appears rarely and only jointly with either Fgl2(+158T/*) or HO-1(−497A/*). All results pertaining to HO-1(−497A/*), either by it self or jointly with other genotypes, indicate that its association with SARS susceptibility is very weak one, if indeed such an association exists. Larger genetic data set is needed to further ascertain its validity, either using this modeling approach or more

traditional statistical analysis which might be more suitable for elucidating the issue at hand, provided a sufficiently large data set is available. Moreover, our study is mainly observational, where no control group who did not get infected with SARS is considered and other likely risk factors have not been controlled for. Since these other factors could have influenced the patient outcomes as well as key rates in our model such as death, incident, and recovery rates, it might have had an effect on our results. In this paper, we have been conservative in reporting statistically significant difference in susceptibility only when there are no overlapping confidence intervals. Note also that this study does not rule out the possibility that other genes may also be associated with susceptibility to SARS.

The model does not consider heterogeneity in contacts, nor do we assign separate compartments for subpopulations such as the healthcare workers. Nosocomial infection played a major role in the SARS outbreak in Taiwan with approximately 80% of the infections occurred in hospitals, out of which roughly 30% were healthcare workers (Ho and Su, 2004). However, since our gene data consists of only 100 cases including 39 healthcare workers, a further division into smaller subgroups of a handful of individuals would render the estimation results highly unreliable. There also may be other unknown factors of social, biological, or environmental nature, which influence SARS susceptibility but are not considered here.

Ideally, it would be much more straightforward, and a stronger test, to go back to the patient samples and type the remaining ones for the three reported SNPs either for statistical association study or present modeling study, especially as apparently less than half of the cases and controls were genotyped. However, that is not feasible in reality. Nevertheless, this work demonstrates the usefulness of mathematical models in molecular epidemiology when only limited partial gene data is available.

Finally, the approach is based on the premise that SARS patients belonging to a given genotype group having a significantly higher SARS infection rate than others would imply that genotype group being less susceptible. There are, clearly, many another factors (e.g., age, gender, social group, etc.) which could affect individual susceptibility to infectious diseases. However, a thorough multivariate analysis which examines all of these factors often requires enormous amount of patient data which is difficult to obtain and typically expensive. A preliminary modeling study of this nature could provide theoretical basis for gene association with particular illness, and to provide justification and unambiguous direction with which more clinical studies can be carried out with appropriate statistical analysis to ascertain the exact association. If a gene association can be affirmed in this manner, it could have important implications for design of intervention strategies for containment of outbreaks, for example, early recognition of those who are most at risk for infection could help disease prevention efforts. Ability to identify those healthcare workers who might have immunoprotection for a particular virus, and who would be most suitable to work and care for the patients in specially designated hospitals for an emerging infectious disease, also could be important especially in times of crisis.

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Appendix

Table A.1 Summary table of 100 confirmed SARS cases by clinical severity and risk genotype frequency of Fgl2(+158T/*), CXCCL10/IP-10(−938AA), and HO-1(−497A/*). One case has no hospitalization data, and hence unknown severity. ("+ + +" denotes presence of genotype at all three genes. "+ − −" denotes presence of the risk genotype at the first gene only. No one has genotype combination of "− + −")

Clinical severity	Genotype combination							Total (%)
	− − −	+ − −	+ + −	− − +	− + +	+ − +	+ + +	
Unknown	1	0	0	0	0	0	0	1
(%)	(0.083)	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)	(0.010)
Mild	6	1	0	9	0	2	0	18
(%)	(0.500)	(0.100)	(0.000)	(0.231)	(0.000)	(0.077)	(0.000)	(0.180)
Intermediate	4	7	1	23	5	16	1	57
(%)	(0.333)	(0.700)	(1.000)	(0.590)	(0.714)	(0.615)	(0.200)	(0.570)
Severe	1	2	0	7	2	8	4	24
(%)	(0.083)	(0.200)	(0.000)	(0.180)	(0.286)	(0.308)	(0.800)	(0.240)
Total	12	10	1	39	7	26	5	100
(%)	(0.120)	(0.100)	(0.010)	(0.390)	(0.070)	(0.260)	(0.050)	(1.000)

Table A.2 Onset-to-hospitalization time (in days) by clinical severity and genotype combination of Fgl2(+158T/*), CXCCL10/IP-10(−938AA), and HO-1(−497A/*) with the standard deviation (SD) given in parenthesis. (One of the 100 cases was omitted due to lack of data)

Genotype combination	Mild		Intermediate		Severe	
	Cases	Onset-to-hospitalization	Cases	Onset-to-hospitalization	Cases	Onset-to-hospitalization
− − −	6	3.1667 (0.3158)	5	1.8000 (0.5556)	1	0
+ − −	1	1.0000	6	2.8333 (0.3529)	2	1.0000
+ + −	0	–	1	7.0000 (0.1429)	0	–
− − +	9	2.5556 (0.3913)	23	3.0870 (0.3239)	7	3.5714 (0.2800)
− + +	0	–	5	2.6000 (0.3846)	2	8.0000 (0.1250)
+ − +	2	1.0000	16	2.4375 (0.4103)	8	2.0000 (0.5000)
+ + +	0	–	1	4.0000 (0.2500)	4	2.5000 (0.4000)

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