Mannose-binding lectin 2 (MBL2) is a serine protease which is believed to be an important factor in the inherited immune system. In this article, we present a coronavirus disease 2019 (COVID-19) family of five patients: a 56-year-old father, a 51-year-old mother, two sons aged 23 and 21 years, and a 15-year-old daughter. According to the results of MBL2 rs1800450 variant analysis performed, the father had homozygous mutant, the mother had homozygous normal, and the three children had heterozygous mutant genotype. When we compared the clinical parameters and genotypes, MBL2 gene polymorphism plays a very important role in COVID-19 susceptibility and severe disease. The family, which makes up our study, is the proof of this situation, and it contains important implications for host factors and COVID-19.
Methods and Results

In this article, the MBL2 (rs1800450) genetic polymorphism was analyzed using the same method, and we present a COVID-19 family of five patients that was proven in parallel with main study. A written consent was obtained from all patients for both sampling and publishing.

The COVID-19 family consisted a total of five members: a 56-year-old father, a 51-year-old mother, two sons aged 23 and 21 years, and a 15-year-old daughter. The father does not have any comorbidities. He was taken to home for isolation on April 2, 2020, after the polymerase chain reaction (PCR) sample was taken in the emergency department, where he presented with symptoms related to upper respiratory tract. Among the PCR samples taken from all patients, only he was positive. On April 7, 2020, all samples were taken again and 23-year-old son was positive. The samples of all family members, together with the father, who admitted to the emergency department on April 9, 2020, with dyspnea and refractory fever, were repeated. The father was hospitalized in the ICU to be followed up with a noninvasive mechanical ventilator in the picture of multi-inflammatory syndrome-adult (MIS-A) with respiratory failure findings. Despite bilateral diffuse lung involvement, the mother without any known comorbidity was taken to the ward due to her vital parameters and clinical stable status. The PCR result taken in the emergency department was positive. The 23-year-old son was hospitalized with bilateral diffuse lung infiltration in the MIS-A picture in ICU. Repeated PCR test is also positive. Of the other two children, the 21-year-old son also showed bilateral lung infiltration, but was only isolated in hospital. The PCR test result was positive. On the other hand, the first PCR test taken in the emergency department of the 15-year-old daughter was negative, but it was decided to be followed up in the hospital due to high risk of contact, and the test repeated 2 days later was found to be positive. The father received anticytokine and anticoagulant treatment during the ICU follow-up; he was discharged after 10 days. The mother and the 23-year-old son were discharged after 7 days with only anticoagulant and supportive treatment, while the 21-year-old son and the 15-year-old daughter were followed up with home isolation after 4 days of anticoagulant and supportive treatments in the hospital. Clinical findings and initial laboratory results are shown in Table 1.

Table 1 Initial clinical and laboratory findings of the family

|                      | Father       | Mother       | 23-year-old son | 21-year-old son | 15-year-old daughter |
|----------------------|--------------|--------------|-----------------|-----------------|----------------------|
| Date of PCR positivity | April 2, 2020 | April 9, 2020 | April 7, 2020   | April 9, 2020   | April 11, 2020       |
| Date of hospitalization | April 9, 2020 | April 9, 2020 | April 9, 2020   | April 9, 2020   | April 9, 2020        |
| Fever                | 39           | 38.3         | 37.8            | 37.5            | 37.8                |
| ABP                  | 138/85       | 125/80       | 130/80          | 120/70          | 120/80              |
| HR                   | 132          | 110          | 130             | 94              | 94                  |
| RR                   | 26           | 14           | 16              | 14              | 16                  |
| OS                   | 84           | 96           | 94              | 98              | 98                  |
| WBC                  | 6,810        | 6,610        | 4,810           | 5,600           | 6,600               |
| Hemoglobin           | 13.1         | 12.3         | 16.4            | 15.6            | 12.4                |
| Neutrophil           | 5,070        | 3,400        | 2,870           | 3,550           | 3,600               |
| Lymphocyte           | 1,290        | 2,800        | 1,560           | 2,000           | 3,000               |
| Platelet             | 221,000      | 416,000      | 139,000         | 318,000         | 214,000             |
| Urea                 | 12           | 23           | 22              | 16              | 18                  |
| Creatinine           | 0.79         | 0.68         | 0.97            | 0.98            | 0.67                |
| LDH                  | 444          | 249          | 327             | 146             | 166                 |
| CRP                  | 10.04        | 0.77         | 23.94           | 4.6             | 2.4                 |
| Ferritin             | 863          | 35.53        | 317.8           | 98              | 66                  |
| AST                  | 42           | 32           | 43              | 22              | 20                  |
| ALT                  | 52           | 22           | 35              | 24              | 24                  |
| D-dimer              | 1.2          | 0.13         | 0.08            | 0.01            | 0.01                |
| CT findings          | Bilaterally involvement | Bilaterally involvement | Bilaterally involvement | Bilaterally involvement | Bilaterally involvement |
| Need for ICU         | Yes          | No           | Yes             | No              | No                  |
| Follow-up duration   | 10           | 7            | 7               | 4               | 4                   |

Abbreviations: ABP, arterial blood pressure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; CT, computed tomography; HR, heart rate; ICU, intensive care unit; LDH, lactate dehydrogenase; OS, oxygen saturation; PCR, polymerase chain reaction; RR, respiratory rate; WBC, white blood cell.
According to the results of \textit{MBL2} (rs1800450) variant analysis performed retrospectively, father had BB (homozygous mutant), mother AA (homozygous normal) and the three children had AB (heterozygous mutant) genotypes (► Fig. 1). 

\textbf{Discussion}

To the best of our knowledge, the COVID-19 family we have reported constitutes the first report in which \textit{MBL2} gene variants are shown. As a summary of studies which investigate the effect of the \textit{MBL2} genotype on gene expression, it was reported that MBL expression in the AB genotype decreased by 1:10, while there was no expression in the BB genotype.\textsuperscript{7,9} In our previous study, it was revealed that patients with BB genotype have a more severe clinical picture. Clinical findings are supported by \textit{MBL2} gene polymorphisms in other studies. In a meta-analysis on severe acute respiratory syndrome coronavirus (SARS-CoV)-1, Middle East respiratory syndrome-related coronavirus, and SARS-CoV-2, 22 out of 32 articles between January 2003 and June 2020 were found to be eligible for review.\textsuperscript{10} As a result of the analysis, it has been determined that \textit{MBL2} gene variants are effective in at least two studies. In another study, Zhang et al examined the frequencies of one mutation in codon 54 and three promoter polymorphisms in nt 550, 221, and four in 352 patients with SARS and 392 healthy controls by using PCR direct sequencing.\textsuperscript{11,12} In this study, codon 54 variant (rs1800450) ownership was associated with decreased \textit{MBL2} expression and SARS-CoV susceptibility. In another study, \textit{MBL2} gene polymorphisms and MBL serum levels were examined.\textsuperscript{12} The distribution of \textit{MBL2} gene polymorphisms was significantly different between SARS patients and the control group, the frequency of haplotypes associated with low or missing MBL serum levels was higher in SARS patients than in the control group. Serum MBL levels were also significantly lower in SARS patients than in the control group.

In the family who was the subject of our study, it is an expected finding that the father has a BB genotype and has the most severe clinical picture. It is thought that the most severe clinical picture after the father, unlike his other siblings, is seen in the 23-year-old son with multiple reasons: he is the first person to become positive after the father and was probably disadvantaged in terms of viral exposure and viral load compared with the other siblings. Because of the gender difference and more importantly, consanguineous marriage between parents, the effects of other possible recessive genes may also have created this difference. The fact that the 15-year-old daughter had the mildest clinical picture, and the disease is thought to be related to the latest PCR positivity and less viral load exposure with isolations. We would like to highlight again that the mother is normal and has a mild life.

\textbf{Conclusion}

As a result, \textit{MBL2} gene polymorphism plays a very important role in terms of COVID-19 susceptibility and severe disease. The family, which makes up our case report, is the proof of this situation, and it contains important implications for host factors and COVID-19.

\textbf{Availability of Data and Materials}

The authors declare that data supporting the findings of this study are available within the referenced articles.

\textbf{Ethical Approval and Consent to Participate}

Ethical committee approval was received (Faculty of Medicine, Istanbul University, approval date and number: 21/05/2020-84539) and a written consent was obtained from all patients for both sampling and publishing. The experimental procedures were based on the Declaration of Helsinki and relevant institutional regulations.

\textbf{Funding}

None.

\textbf{Conflict of Interest}

None declared.

\textbf{References}

\textsuperscript{1} Cai Q, Chen F, Wang T, Luo F, Liu X, Wu Q, et al. Obesity and COVID-19 Severity in a Designated Hospital in Shenzhen, China. Diabetes Care 2020;43(07):1392–1398
2 Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al; China Medical Treatment Expert Group for Covid-19. Clinical characteristics of coronavirus Disease 2019 in China. N Engl J Med 2020;382(18):1708–1720
3 Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med 2020;180(07):934–943
4 Jacobson S, Larsson P, Åberg AM, Johansson G, Winsö O, Söderberg S. Levels of mannose-binding lectin (MBL) associates with sepsis-related in-hospital mortality in women. J Inflamm (Lond) 2020;17:28
5 Best LG, Ferrell RE, Decroo S, North KE, Maccluer JW, Zhang Y, et al. Genetic and other factors determining mannose-binding lectin levels in American Indians: the Strong Heart Study. BMC Med Genet 2009;10:5
6 Eisen DP, Minchinton RM. Impact of mannose-binding lectin on susceptibility to infectious diseases. Clin Infect Dis 2003;37(11):1496–1505
7 Medetaliyoglu A, Bahat G, Senkal N, Kose M, Avci K, Sayin GY, et al. Mannose binding lectin gene 2 (rs1800450) missense variant may contribute to development and severity of COVID-19 infection. Infect Genet Evol 2021;89:104717
8 Sumiya M, Super M, Tabony P, Levinsky RJ, Arai T, Turner MW, et al. Molecular basis of opsonic defect in immunodeficient children. Lancet 1991;337(8757):1569–1570
9 Madsen HO, Garred P, Kurtzhals JA, Lamm LU, Ryder LP, Thiel S, et al. A new frequent allele is the missing link in the structural polymorphism of the human mannann-binding protein. Immunogenetics 1994;40(01):37–44
10 Di Maria E, Latini A, Borgiani P, Novelli G. Genetic variants of the human host influencing the coronavirus-associated phenotypes (SARS, MERS and COVID-19): rapid systematic review and field synopsis. Hum Genomics 2020;14(01):30
11 Zhang H, Zhou G, Zhi L, Yang H, Zhai Y, Dong X, et al. Association between mannose-binding lectin gene polymorphisms and susceptibility to severe acute respiratory syndrome coronavirus infection. J Infect Dis 2005;192(08):1355–1361
12 Ip WK, Chan KH, Law HK, Tso GH, Kong EK, Wong WH, et al. Mannose-binding lectin in severe acute respiratory syndrome coronavirus infection. J Infect Dis 2005;191(10):1697–1704