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Letter

The Effect of HLA-B27 on Susceptibility and Severity of COVID-19

To the Editor:

Although many genes have polymorphisms, major histocompatibility complex genes are the most polymorphic. Many assume that the diversity of HLA increases the likelihood that a species can survive pandemics. Indeed, evidence suggests that HLA-B27 is protective for HIV[1], hepatitis C[2], and possibly influenza[3]. We recently reported results of a Web-based survey involving patients with spondyloarthritis (SpA)[4]. We now report an additional analysis of these data obtained between April 10, 2020, and May 31, 2020, to determine if the genetic marker HLA-B27 influences the contracting of the coronavirus 2019 (COVID-19) or the severity of COVID-19 infection.

Subjects who participated in this research provided electronic consent as a first step in completing the survey. As it was a survey, it was not practical to obtain written, informed consent. Institutional review board approval was received from Oregon Health & Science University (IRB approval number: 00021375).

Subjects (n = 3435) from 65 countries diagnosed with SpA completed the survey. Of these, 2836 or 82.6% were aware of their HLA-B27 status, with 76.1% being positive. Of those with known HLA-B27 status, 74.5% were from the United States and 8.0% were from Canada. The median age was 52 years. The group aware of B27 status included 1806 women, 1015 men, and 15 nonbinary. Interestingly, 82.9% of male respondents were HLA-B27+ compared to 72.2% of female respondents. It has been previously noted that women with ankylosing spondylitis (AS) are less likely to be B27+ compared to men[5]. Table 1 shows the specific diagnoses and the HLA-B27 status for each diagnosis. Subjects with acute anterior uveitis had the highest percentage who were known to be B27-positive (calculated on the basis of only those who knew their B27 status) at 87.4%. Surprisingly, AS at 79.3% was slightly less likely to be associated with HLA-B27 than reactive arthritis, but the survey included relatively few with reactive arthritis. As expected, fewer with nonradiographic axial SpA were HLA-B27–positive (65.8%) compared to AS. Crohn disease, ulcerative colitis, and psoriasis are not associated with HLA-B27. However, a high percentage of respondents with one of these diagnoses was HLA-B27–positive. This high percentage undoubtedly reflects the nature of the survey and meant that anyone with one of these diagnoses also had SpA.

Forty-one subjects reported having COVID-19, although only 18 reported testing positive. Many reporting agencies now announce presumed as well as confirmed cases since PCR testing is not universal. Ten of 679 B27-negative subjects (1.5%) believed they had had COVID-19, whereas 31 of 2157 B27-positive subjects believed that they had COVID-19 (1.4%). This difference is not significantly different by the chi-square test ($P = 0.112$). If one restricts the analysis to those with a positive test for the virus, the result was 0.6% for either B27-negative or B27-positive subjects.

We assessed COVID-19 severity on a subjective scale ranging from 1 (mild) to 10 (life-threatening) and found no significant effect from B27, whether the analysis was based on confirmed or suspected cases. The distribution of COVID-19 severity based on suspected cases is shown in Table 2.

There were only 5 hospitalizations among the respondents: 1 of 679 who was HLA-B27–negative and 4 of the 2157 who were HLA-B27–positive. This difference is also not statistically significant.

The extensive polymorphism of the HLA system is thought to result from the need for a species to be immunologically diverse in order to survive a pandemic. HLA-B27 confers some protection against HIV[3] and hepatitis C[4]. However, it does not appear to protect against severe acute respiratory syndrome[6,7], which like COVID-19, is attributable to coronavirus. Our data are consistent with another recent study, which did not report on spondylitis specifically, but relative to other rheumatic diseases, spondylitis did not appear to confer unique susceptibility or result in greater severity from COVID-19[8]. We believe that ours is the first study to specifically address the consequences of being HLA-B27–positive in relation to this infection.

This study has several limitations. Although we surveyed a large number of patients with SpA, we identified a relatively small number of subjects with a confirmed COVID-19 infection. However, the rate of infection among our US respondents, 5.69 cases per 1000 people, is very comparable to the expected rate in the United States of 5.35 cases per 1000 as of May 31, 2020.

Table 1. Diagnoses included in survey and relation to HLA-B27.

Diagnosis	Frequency of Diagnosis Among Respondents With Known HLA-B27 Status, %	Frequency of HLA-B27 Positivity for Given Diagnosis, %
Acute anterior uveitis	21.6	87.4
Ankylosing spondylitis	86.0	79.3
Arthritis with IBD	5.5	68.8
Crohn disease	4.6	70.2
Juvenile AS	1.4	85.3
Nonradiographic axial SpA	6.8	65.8
Peripheral SpA	6.5	67.2
Psoriasis	6.8	72.7
Psoriatic arthritis	7.5	59.4
Reactive arthritis	3.7	82.7
Ulcerative colitis	4.5	65.6
Undifferentiated SpA	8.0	55.7

Note that a subject could have > 1 diagnosis, such as acute anterior uveitis and AS. AS: ankylosing spondylitis; IBD: inflammatory bowel disease; SpA: spondyloarthritis.

Table 2. Effect of B27 status on subjective severity of symptoms attributed to COVID-19*.

	HLA-B27– negative, n (%)	HLA-B27– positive, n (%)
1 (extremely mild symptoms)	0 (0.0)	1 (3.2)
2	1 (10.0)	1 (3.2)
3	2 (20.0)	3 (9.7)
4	2 (20.0)	2 (6.5)
5	1 (10.0)	6 (19.4)
6	1 (10.0)	5 (16.1)
7	1 (10.0)	6 (19.4)
8	2 (20.0)	4 (12.9)
9	0 (0.0)	2 (6.5)
10 (life-threatening symptoms)	0 (0.0)	1 (3.2)

*COVID-19 diagnosis not always confirmed. Values are n (%) with either confirmed or unconfirmed COVID-19 infection and their subjective score for the severity of the COVID-19 infection. The difference between HLA-B27–negative and HLA-B27–positive is not statistically significant based on the Pearson chi-square test with simulated *P* value (based on 2000 replicates; $P = 0.867$). COVID-19: coronavirus disease 2019.

Thus, while our observations should be replicated and confirmed, they are consistent with expected values for the United States as a whole. Second, we tested for the effect of HLA-B27 in the context of SpA. Although we do not currently suspect that SpA or the medications taken for SpA affect the likelihood of developing COVID-19[4,8,9], it is possible that a study on healthy HLA-B27 individuals might find differences not detectable with our methodology. Finally, only HLA-B27 alleles could be analyzed, and other HLA-B alleles have been shown to influence the risk for AS, such as B*38 and B*40[10]. These alleles should be further examined for potential effect on COVID-19. We are collecting longitudinal data on the subjects in this study to gain more information as to how HLA-B27–related disease affects COVID-19 susceptibility or severity.

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