

# Study provides a genetic explanation for asymptomatic COVID infection

Bill Shaw  
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An international collaboration of researchers recently published a study that conclusively demonstrated a biological explanation for how a human genetic variation known as the *HLA-B\*15:01* allele results in a much higher likelihood of asymptomatic infection with SARS-CoV-2, the virus that causes COVID-19. The study not only found a strong association of the *HLA-B\*15:01* allele with asymptomatic SARS-CoV-2 infection, it also subsequently elucidated the biological mechanism that explains the association.

‘HLA’ stands for ‘human leukocyte antigen’ and thus HLA genes are directly involved in human immune responses to infection (‘leukocyte’ is the medical term for the white blood cells that fight infections in the body). Prior research on viral infections has shown that varying HLA alleles are associated with differential responses and outcomes to infections with human immunodeficiency viruses and hepatitis viruses.

The researchers first studied the association with carrying at least one *HLA-B\*15:01* allele and the odds of having an asymptomatic infection. They demonstrated the association in one dataset, and then confirmed it in an additional two datasets. These “replication cohorts,” as they are called, are a key methodology in genetic and genomic studies and strengthen the results of the study considerably.

Across all three cohorts—the initial cohort and two replication cohorts, a meta-analysis showed that individuals with an *HLA-B\*15:01* allele were 2.55 times more likely (95% confidence interval of 1.73 to 3.77) to experience asymptomatic infection than individuals without *HLA-B\*15:01*. In the first cohort, individuals who were homozygous—that is, they had two *HLA-B\*15:01* alleles—were 8.58 times more likely to have an asymptomatic infection.

Overall, the researchers found that 20 percent of individuals with asymptomatic infection were carriers of *HLA-B\*15:01* versus 9.4 percent of symptomatic individuals. This finding was replicated in both additional cohorts, with rates of 17 percent of asymptomatic versus 7 percent of symptomatic, and 25 percent asymptomatic versus 9.4 percent of symptomatic as carriers, respectively.

The researchers went on to show that no other HLA allele was significantly associated with asymptomatic infection. Furthermore, they looked at interactions among HLA alleles by studying all possible pairs of HLA alleles. They found that only one such pairing was significantly associated with asymptomatic infection: the pair of *HLA-B\*15:01* and *HLA-DRB1\*04:01*. Individuals with this pairing were 3.17 times more likely to have asymptomatic SARS-CoV-2 infection, suggesting that the effect of *HLA-B\*15:01* is enhanced by additionally having *HLA-DRB1\*04:01*.

The researchers subsequently went on to demonstrate the biological mechanism by which such protection of *HLA-B\*15:01* carriers occurs. This work is an enormous strength of the study and makes its results even stronger.

At a high level, the mechanism is that individuals with *HLA-B\*15:01* who were previously exposed to seasonal, pre-pandemic coronaviruses had memory T cells which were highly activated by SARS-CoV-2 proteins. This “cross-reactivity” was mediated by two SARS-CoV-2 proteins, NQK-K8 and NQK-A8, and it was specific to prior exposure to seasonal coronaviruses OC43-CoV and HKU1-CoV.

The fact that the T cells were highly reactive means that they divided rapidly, making copies of themselves for distribution throughout the body to recognize and neutralize virus and virus-infected cells. Early

activation of memory T cells is thus associated with rapid clearing of infection and reduced duration and severity of illness.

The researchers demonstrated such T cell reactivity from blood specimens they had taken from participants prior to the onset of the pandemic. This showed that memory T cells sensitized to proteins from seasonal coronaviruses OC43-CoV and HKU1-CoV reacted strongly to the NQK-K8 and NQK-A8 proteins of SARS-CoV-2. By using samples obtained prior to the onset of the pandemic, the researchers left no chance for bias or contamination by “apparently” unexposed individuals who had really been exposed to SARS-CoV-2.

The researchers then were able to study the three-dimensional conformation of the peptide transcribed from *HLA-B\*15:01* —also called HLA-B\*15:01—in combination with the NQK-K8 peptide and with the NQK-A8 peptide of SARS-CoV-2. They demonstrated that HLA-B\*15:01 clearly binds both NQK-K8 and NQK-A8 at its major binding site, necessary to induce an immune reaction of the T cell.

Furthermore, the three-dimensional conformations of HLA-B\*15:01/NQK-K8 and HLA-B\*15:01/NQK-A8 are nearly identical, with a deviation metric of only 0.08 Angstroms (10<sup>-10</sup> meters) at the cleft in HLA-B\*15:01 where it binds each peptide. This means that the binding of either peptide will produce a highly similar immune response.

It is notable that NQK-K8 differs from the peptide of OC43-CoV and HKU1-CoV by only one amino acid (the basic building block of peptides). Also, NQK-K8 is conserved (the same) across all variants of SARS-CoV-2, including the XBB variant that until recent weeks was predominant globally. Thus, the results of the study are applicable across all variants of SARS-CoV-2 up to and including XBB.

This study adds to the irrefutable evidence that asymptomatic infection occurs, and it is convincing evidence that individuals’ genetic makeup is a significant factor in whether they experience asymptomatic infection. Given that asymptomatic individuals are a known significant source of SARS-CoV-2 transmission, this study further justifies properly executed lockdowns, masking, and social distancing measures as necessary components of an overall COVID-19 eradication program.

Also, asymptomatic infection is not consequence free. One study that pooled results from multiple previous studies found that 17 percent of asymptomatic individuals had at least one long-term sequelae at one year after infection. That means that between 1 in 5 and 1 in 6 individuals who had no symptoms of their acute SARS-CoV-2 infection are impacted longer term.

Ultimately, the study adds to the growing evidence of the ruling class’s criminality in implementing a series of reckless policies designed to maximize the production of profits, not aimed at the eradication of the SARS-CoV-2 virus.



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