Lack of association between HLA and asymptomatic SARS-CoV-2 infection

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Abstract

Human genetic studies of critical COVID-19 pneumonia have revealed the essential role of type I interferon-dependent innate immunity to SARS-CoV-2 infection. Conversely, an association between the HLA-B*15:01 allele and asymptomatic SARS-CoV-2 infection in unvaccinated individuals was recently reported, suggesting a contribution of pre-existing T cell-dependent adaptive immunity. We report a lack of association of classical HLA alleles, including HLA-B*15:01, with pre-omicron asymptomatic SARS-CoV-2 infection in unvaccinated participants in a prospective population-based study in the US (191 asymptomatic vs. 945 symptomatic COVID-19 cases). Moreover, we found no such association in the international COVID Human Genetic Effort cohort (206 asymptomatic vs. 574 mild or moderate COVID-19 cases and 1,625 severe or critical COVID-19 cases). Finally, in the Human Challenge Characterisation study, the three HLA-B*15:01 individuals infected with SARS-CoV-2 developed symptoms. As with other acute primary infections, no classical HLA alleles favoring an asymptomatic course of SARS-CoV-2 infection were identified. These findings suggest that memory T-cell immunity to seasonal coronaviruses does not strongly influence the outcome of SARS-CoV-2 infection in unvaccinated individuals.

Introduction

Primary infection with SARS-CoV-2 underlies a broad spectrum of clinical manifestations in unvaccinated individuals, ranging from silent infection to lethal COVID-19 pneumonia. Rare and common human genetic variants have been associated with hypoxemic COVID-19 pneumonia [1–5]. Inborn errors of TLR3- and/or TLR7-dependent type I IFN immunity in respiratory epithelial cells and plasmacytoid dendritic cells underlie critical COVID-19 pneumonia in 1-5% of cases [1,6–8]. Moreover, autoantibodies neutralizing type I interferon (IFN) underlie at least another 15% of cases [9–11], further highlighting the key role of type I IFNs in protective immunity to SARS-CoV-2 infection in the respiratory tract. Inborn errors of the OAS-RNase L pathway underlie MIS-C in about 1% of cases [12], but the other manifestations of SARS-CoV-2 infection remain unexplained (COVID toes, long COVID etc.). In the large sample study from the COVID-19 Host Genetics Initiative, only one human leukocyte antigen (HLA) class II allele, HLA-DRB1*04:01, has been found to confer a small decrease in the risk of critical COVID-19 (OR = 0.8) [2]. By contrast, we have documented a stronger association between HLA-A*03:01 and side effects following inoculation with the Pfizer-BioNTech COVID-19 mRNA vaccine [13], which was subsequently replicated [14].

In this context, in July 2023, an association was reported between the HLA-B*15:01 allele and asymptomatic SARS-CoV-2 infection in unvaccinated individuals [15]. The OR was 2.40 (95%CI: 1.54–3.64) for heterozygotes, reaching 8.58 (95%CI: 1.74–34.43) in homozygotes. Silent SARS-CoV-2 infection had not hitherto been explicitly studied as a phenotype in large genetic studies. This study further showed that T-cells from HLA-B*15:01 individuals who had not been infected with SARS-CoV-2 recognized a SARS-CoV-2 T-cell epitope by cross-reactivity due to prior exposure to one of two common cold coronaviruses: OC43-CoV or HKU1-CoV[15]. Moreover, more than 100 immunogenic SARS-CoV-2 peptides are highly similar to peptides from at least one human coronavirus (hCoV) presented by a wide range of classical HLA molecules [16]. We, therefore, tested the hypothesis of an association between HLA alleles and asymptomatic SARS-CoV-2 infection in two large independent cohorts. We aimed: (i) to test the association with HLA-B*15:01 and (ii) to identify additional HLA alleles potentially associated with asymptomatic COVID-19.

Material and methods

Cohorts and phenotype information

US prospective cohort

Participants in the US prospective cohort came from two studies: the Helix DNA Discovery Project and the Healthy Nevada Project. All the enrolled participants provided written informed consent for participation and were recruited through protocols conforming to local ethics requirements. The Helix DNA Discovery Project was reviewed and approved by the Western Institutional Review Board. For the Healthy Nevada Project (HNP), the University of Nevada, Reno Institutional Review Board approved the study (project 956068-12). The procedures followed were in accordance with ethical standards, and appropriate informed consent was obtained. We performed an online survey that we sent a few times in 2021. The survey takes about 15 minutes to complete and has been published in the past [13]. We received responses from 8,125 unique Helix DNA Discovery Project participants and 9,315 unique Healthy Nevada Project participants. The participants in this cohort were 18 to 89+ years old, 65% were female, and 85% were of European genetic ancestry. The respondents indicated whether they had been infected and whether they had been vaccinated, as well as information on exposure, reasons for testing, and comorbidities. They rated the severity and duration of their symptoms and disease. They answered questions about 24 specific symptoms known to occur after SARS-CoV-2 infection.

CHGE cohort

Since the beginning of the pandemic, the COVID Human Genetic Effort (CHGE) has enrolled more than 10,000 individuals with SARS-CoV-2 infection and broad clinical manifestations from all over the world. All the enrolled participants provided written informed consent for participation and were recruited through protocols conforming to local ethics requirements. For patients enrolled in the French COVID cohort (ClinicalTrials.gov NCT04262921), ethics approval was obtained from the Comité de Protection des Personnes Ile De France VI (ID RCB, 2020-A00256-33) or the Ethics Committee of Erasme Hospital (P2020/203). For participants enrolled in the COV-Contact study (ClinicalTrials.gov NCT04259892), ethics approval was obtained from the CPP IDF VI (ID RCB, 2020-A00280-39). For patients enrolled in the Italian cohort, ethics approval was obtained from the University of Milano-Bicocca School of Medicine, San Gerardo Hospital, Monza–Ethics Committee of the National Institute of Infectious Diseases Lazzaro Spallanzani (84/2020) (Italy), and the Comitato Etico Provinciale (NP 4000–Studio CORONAlab). STORM-Health care workers were enrolled in the STudio OsseRvazionale sullo

screening dei lavoratori ospedalieri per COVID-19 (STORM-HCW) study, with approval from the local institutional review board (IRB) obtained on June 18, 2020. Patients and relatives from San Raffaele Hospital (Milan) were enrolled in COVID-BioB/Gene-COVID protocols and, for additional studies, TIGET-06, with the approval of the local ethics committee. Patients and relatives from Rome were enrolled in Protocol no. 50/20 (Tor Vergata University Hospital). Informed consent was obtained from each patient. For the patients enrolled in the COVIDeF Study Group (ClinicalTrials.gov NCT04352348), ethics approval was obtained from the Comité de Protection des Personnes Ile de France XI (ID RCB, 2020-A00754-35). For patients enrolled in Spain, the study was approved by the Committee for Ethical Research of the Infanta Leonor University Hospital, code 008–20; the Committee for Ethical Research of the 12 de Octubre University Hospital, code 16/368; the Bellvitge University Hospital, code PR127/20; the University Hospital of Gran Canaria Dr. Negrín, code 2020–200-1 COVID-19; and the Vall d'Hebron University Hospital, code PR(AMI)388/2016. Anonymized samples were sequenced at the National Institute of Allergy and Infectious Diseases (NIAID) through the Uniformed Services University of the Health Sciences (USUHS)/the American Genome Center (TAGC) under nonhuman subject research conditions; no additional IRB consent was required at the National Institutes of Health (NIH). For patients enrolled in the Swedish COVID cohort, ethics approval was obtained from the Swedish Ethical Review Agency (2020–01911 05).

The physicians classified the patients as follows: i) Critical cases were defined as patients with pneumonia requiring high-flow oxygen (> 6 L/min) and/or requiring admission to the intensive care unit; ii) Severe cases were defined as patients with pneumonia requiring low-flow oxygen (< 6 L/min); iii) Moderate cases were defined as patients with ambulatory pneumonia; iv) Mild cases were defined as pauci-symptomatic patients, with the presence of mild, self-healing symptoms such as cough, fever, body aches, anosmia; and v) Asymptomatic cases were defined as infected individuals with no symptoms. The presence of infection was assessed on the basis of a positive PCR test and/or serological test and/or the presence of typical symptoms such as anosmia or ageusia after exposure to a confirmed COVID-19 case.

SARS-CoV-2 Human Challenge Characterisation Study

34 participants seronegative to spike protein were challenged with D614G-containing pre-Alpha SARS-CoV-2, of whom 33 consented for genetic analysis. Additional details on the study design and participants were previously published [17]. Ethics approval was obtained from the UK Health Research Authority Ad Hoc Specialist Ethics Committee (reference: 20/UK/0002). Written informed consent was obtained from participants before screening and enrollment.

Sequencing

US prospective cohort

DNA samples were sequenced and analyzed at Helix with the Exome+® assay as previously described [18]. Genotype processing was performed in Hail [19].

CHGE cohort

Whole-exome (WES) or whole-genome sequencing (WGS) was performed at several sequencing centers, including the Genomics Core Facility of the Imagine Institute (Paris, France), the Yale Center for Genome Analysis (USA), Macrogen (USA), Psomagen (USA), the New-York Genome Center (NY, USA), TAGC (USUHS, Bethesda, USA), MNM Bioscience (Poland), Invitae (San Francisco, USA), the Genomic Sequencing Platform Seqoia (France), the Centre National de Recherche en Génomique Humaine (CNRGH, Evry, France), the Genomics Division-ITER of the Canarian Health System sequencing hub (Canary Islands, Spain), and the AlJalila Genomics Center (Dubai). Libraries for WES were generated with the Twist and Twist Plus Human Core Exome Kit, the xGen Exome Research Panel from Integrated DNA Technologies (IDT; xGen V1 and V2), Agilent SureSelect (Human All Exon V6 and V7) panels, the SeqCap EZ MedExome Kit from Roche, the Nextera Flex for Enrichment-Exome kit, the Illumina TruSeq Exome panel and WES custom target enrichment probes. Massively parallel sequencing was performed on HiSeq 4000, HiSeq 2500, NextSeq 550 or NovaSeq 6000 systems (Illumina).

For principal component analysis (PCA), common variants from the gnomAD v2.1 Exome dataset were jointly genotyped with GATK GenotypeGVCFs. PCA was performed with PLINK v1.9 software on a pruned set of ~14,600 SNPs not in linkage disequilibrium (maximum r2 value for linkage disequilibrium of 0.4 between pairs of SNPs), with a minor allele frequency (MAF) > 1%, a call rate > 99%, and P value for departure from Hardy–Weinberg equilibrium > 10e−5, as previously described [20]. The ancestral origin of the patients was further inferred from the PCA, as previously described [20].

SARS-CoV-2 Human Challenge Characterisation Study

Whole-genome sequencing was performed on Illumina NovaSeq (Novogene Ltd., IK), yielding 150bp paired-end reads. The average depth of coverage was > 50x with a minimum of 31x. PCA and global ancestry inference were performed using Hail according to the protocol described by the gnomAD project [21].

HLA calls / imputation

US prospective cohort

HLA types for A, B, C, DPB1, DQA1, DQB1, and DRB1 were imputed with HIBAG using the default recommendations [22]. Individual genotypes were imputed with the model for the most appropriate genetic ancestry for each individual. Probabilities greater than 0.5 were used for genotype calling.

CHGE cohort

Classical class I and class II HLA alleles were typed from the raw WES or WGS reads with HLA*LA software [10], which uses a linear projection method to align reads to a population reference graph and enables high HLA typing accuracy from WES or WGS data.

SARS-CoV-2 Human Challenge Characterisation Study

HLA alleles were typed from raw WGS reads with HLA*LA software at G group resolution. Only HLA calls with a posterior probability of 100% and a minimum coverage of 20x were retained in the analysis. At the B locus, all individual calls fulfilled these filtering criteria at 2-field resolution.

These tools have been validated for their accuracy to call HLA alleles at 2-field resolution, particularly in populations of European ancestry. For example, the HIBAG HLA calls made at Helix for 7 genes in 7 European ancestry Coriell samples showed 99% concordance with the known HLA calls for these individuals. Differences caused by HLA allele calling should mostly be limited to rare HLA types and populations with poor imputation references.

HLA-WAS

We used Regenie [23] for the genetic analysis. In brief, this method builds a whole-genome regression model based on common variants to account for the effects of relatedness and population stratification; it also accounts for situations in which there is an extreme case-control imbalance likely to lead to test statistic inflation with other analysis methods. We used the approximate Firth p value when the logistic regression p value was below 0.01. The covariates included were age group, sex and the first five principal components.

For the US prospective cohort, a representative set of 184,445 coding and noncoding LD-pruned, high-quality common variants were identified for the construction of PCs and the whole-genome regression model, as previously described [18]. PCs were calculated within the European group. For CHGE, the set of ~14,600 SNPs used for PCA within the European group was used for the whole-genome regression model.

Meta-analysis

Results were combined by inverse variance-weighted fixed-effects meta-analysis with METAL [24]. Effect was provided as the BETA value and the STDERR was provided as the SE.

Power calculation

We estimated the power required to detect an effect similar to that reported by Augusto, Murdolo & Chatzileontiadou et al. with the Genetic Association Study (GAS) Power Calculator, which uses a method derived from the CaTS power calculator for two-stage association studies [25]. The parameters used were: HLA-B*15:01 frequency: 0.05; prevalence of asymptomatic infection: 0.1; Dominant inheritance model; p-value threshold = 0.05; numbers of cases and controls according to the third definition in both cohorts.

Serology

Plasma IgG titres were determined using MesoScale Discovery Coronavirus panel 2 plates on a SQ120 instrument. Binding titres given as arbitrary units per milliliter (AU/ml) based on a kit-provided human plasma standard curve.

Results

US prospective cohort description

We first conducted an HLA-wide association study (HLA-WAS) in a prospective population-based US cohort (**Figure 1**). Participants were either part of the Helix DNA Discovery Project or the Healthy Nevada project, and were recruited before the start of the COVID-19 pandemic. All participants underwent Exome+® sequencing, which targets the exome and a few hundred thousand non-exonic common SNPs, providing a backbone for imputation of the most common SNPs in the genome. HLA alleles were called for seven genes (HLA -A, -B, -C, -DPB1, -DQA1, -DQB1, and -DRB1) with HIBAG [22]. The 17,434 adults who responded to at least one of the COVID-19 infection and vaccination surveys sent in 2021 included 1,680 participants reporting SARS-CoV-2 infection while unvaccinated. A continuous spectrum of symptoms, duration of illness was reported following SARS-CoV-2 infection (**Figure S1**). The most common symptoms were muscle and body aches, and a cough (**Figure S1A**). No symptoms at all were reported by 5.1% of individuals (n=86), whereas 5.3% of the infected participants required

hospitalization with or without oxygen therapy (n=58) or were admitted to the intensive care unit (n=31) (**Figure S1B**).

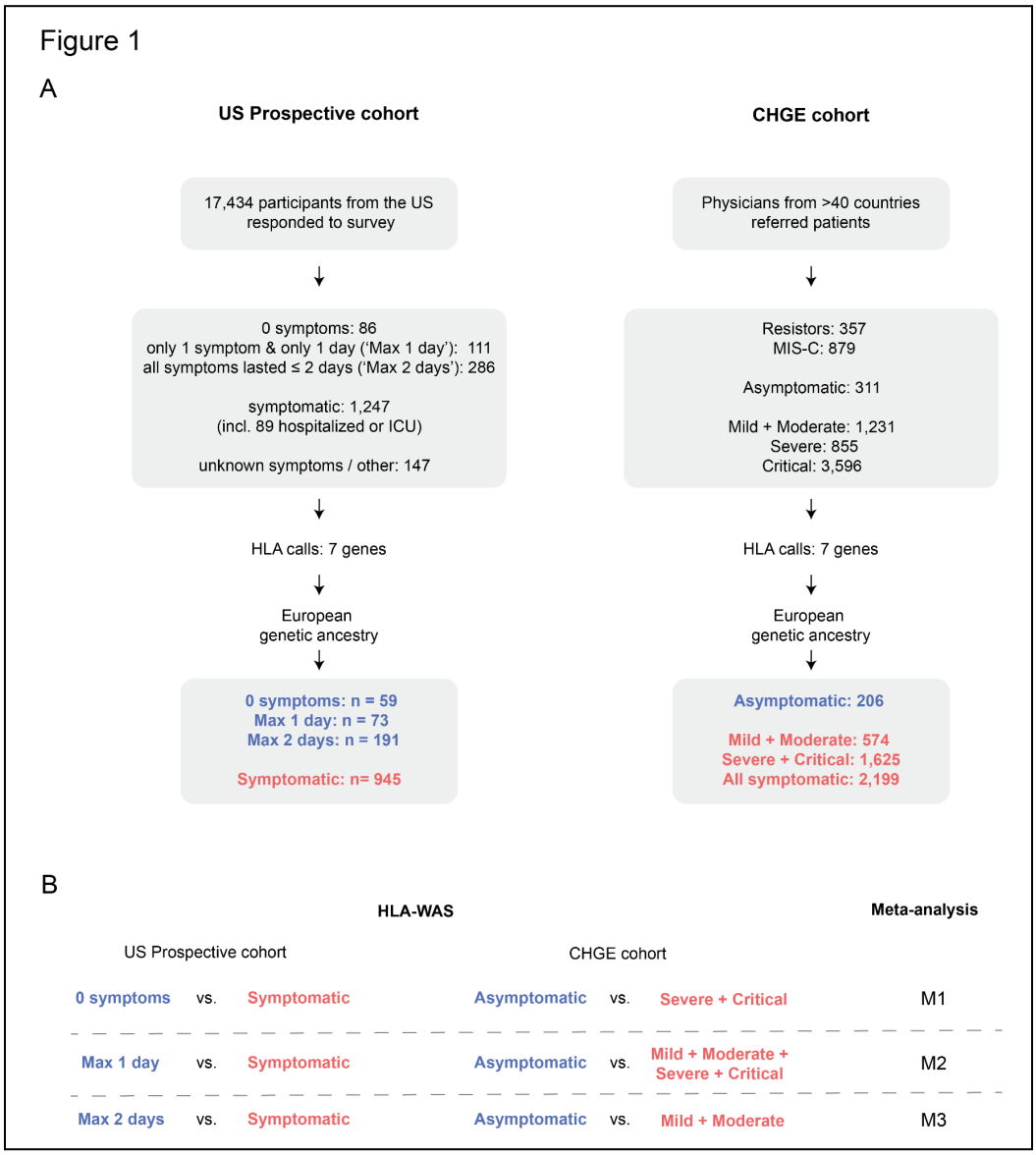

Figure 1: Study design.
A: Description of the two cohorts and definitions of asymptomatic and symptomatic cases.
B: List of HLA-wide association studies and meta-analyses performed.

HLA-wide association in the US prospective cohort

We tested the hypothesis that HLA alleles play an important role in the early response to SARS-CoV-2 by considering three case definitions for the asymptomatic cases (**Figure 1A**): 1) '0 symptoms' was a stringent definition of asymptomatic as a total absence of symptoms (n=86); 2) 'Max 1 day' was a definition of asymptomatic in which the presence of one symptom

for no more than one day was tolerated (n=111). This definition was used to increase the power for detection of an association by enlarging the 'asymptomatic' group whilst still identifying individuals who cleared the virus quickly and efficiently; 3) 'Max 2 days' was a definition as close as possible to that used by Augusto, Murdolo & Chatzileontiadou et al., considering participants to be asymptomatic if none of their symptoms lasted three days or more, and if the reason for testing was unrelated to symptoms (n=286) [15]. We used only one definition for controls (individuals with symptoms lasting at least three days). The control group included all individuals admitted to the ICU or the hospital and anyone reporting symptoms of at least three days' duration with some impact on their daily routine (n=1,247). For the HLA-WAS, we restricted the analysis to individuals with a genetically inferred European ancestry (**Figure S1C-D**), leading to a total of 59 to 191 asymptomatic cases and of 945 symptomatic controls (**Figure 1A**). Age and sex distribution are shown in **Table S1**. The association test was performed with Regenie [23] under a dominant inheritance model, with age, sex and the first five principal components as covariates (see **Supplemental methods**). The risk of detecting false positive associations was decreased by limiting the analysis to the 105 HLA alleles with an allele frequency of at least 1% in this cohort. No statistically significant associations (at a corrected threshold of $p<0.00047$) were found with any of the three phenotype definitions (**Table 1**, **Tables S2-4**). The top-ranked HLA allele was DRB1*16:01, which was depleted in asymptomatic individuals, with the strongest effect being observed in the 'Max 2 days' group of asymptomatic patients (OR [95%CI] = 0.06 [0 – 1.5], p=0.004, **Table 1**).

Table 1: Top-ranked alleles in the HLA-WAS on the US prospective cohort.

Allele	OR [95% CI][a]	p value	AF[b]	Asymptomatic definition[c]
DRB1*16:01	0.06 [0.002-1.5]	0.004	0.012	Max 2 days
A*32:01	2.19 [1.3-3.8]	0.008	0.035	Max 2 days
B*07:02	1.58 [1.1-2.3]	0.016	0.13	Max 2 days
C*07:02	1.53 [1.1-2.2]	0.020	0.14	Max 2 days
DQB1*06:02	1.52 [1.1-2.2]	0.025	0.14	Max 2 days
DQB1*05:02	0.29 [0.1-1.1]	0.037	0.015	Max 2 days

[a] Odds ratio (OR) of being asymptomatic, i.e. OR>1 indicates that the allele is more frequent in asymptomatic individuals. CI: confidence interval.

[b] Allele frequency (AF) is based on the frequency of the allele in the US prospective cohort 'Max 2 days' analysis because this analysis included the largest numbers of cases and controls.

[c] For each allele, the top-ranked result across the three asymptomatic definitions in the US prospective cohort is given.

HLA-wide association in the CHGE cohort

We next studied patients recruited by the physicians of the international CHGE consortium. These physicians classified participants with SARS-CoV-2 infections according to acute disease severity: asymptomatic, mild, moderate, severe, or critical (**Figure S2A**). Whole-exome or whole-genome sequencing data were available for 7,229 participants and HLA alleles were typed with HLA*LA [26]. In this HLA-WAS, we compared the patients classified as 'asymptomatic' by the clinicians (n=311) with those in three sets of symptomatic controls: 1) the patients with the most extreme symptoms requiring hospitalization and oxygen supplementation (i.e. those with a severe or critical form of the disease, n=4,451); 2) all symptomatic patients, whatever their acute disease severity (i.e. mild, moderate, severe or critical, n=5,682); and 3) symptomatic patients not requiring oxygen supplementation (i.e. mild and moderate patients only, n=1,231); this last group of symptomatic patients is the most similar to the symptomatic patients groups of the US prospective cohort and the study by Augusto, Murdolo & Chatzileontiadou et al. (**Figure 1**). We restricted the analysis to individuals of European genetic ancestry and the final study population comprised 206 asymptomatic cases, 1,625 patients with severe or critical disease and 574 patients with mild or moderate disease **(Figure S2B-C**). Age and sex distribution are shown in **Table S1**. Analyses were also performed under a dominant inheritance model with age group, sex and the first five principal components as covariates. This analysis was performed with Regenie and was limited to the 117 HLA alleles with an allele frequency of at least 1% in this cohort. No statistically significant association (at a corrected threshold of $p<0.00043$) was identified in the HLA-WAS, regardless of the definition of symptomatic patients used (**Tables S5-S7**). The top-ranked HLA allele found to be enriched in asymptomatic individuals was HLA-B*40:02, for which the strongest effect was observed in comparison with the group of symptomatic patients with severe or critical disease (OR [95%CI] = 3.4 [1.5 – 7.7], p=0.005, **Table 2**).

Table 2: Top-ranked alleles in the HLA-WAS on the CHGE European cohort.

Allele	OR [95% CI][a]	p value	AF[b]	Controls used[c]
B*40:02	3.42 [1.5-7.7]	0.005	0.016	Severe + Critical
DPB1*01:01	0.28 [0.1-0.8]	0.007	0.042	Severe + Critical
A*23:01	2.5 [1.2-5.0]	0.010	0.023	Mild + Moderate
B*49:01	2.26 [1.2-4.3]	0.014	0.031	Mild + Moderate
A*03:01	1.66 [1.1-2.5]	0.019	0.12	Severe + Critical

DQA1*01:02	1.54 [1.1-2.2]	0.022	0.18	Mild + Moderate
A*30:02	2.46 [1.1-5.6]	0.031	0.019	Mild + Moderate
B*57:01	0.47 [0.2-1.0]	0.047	0.027	Mild + Moderate
A*68:02	3.53 [1.0-12.2]	0.047	0.01	Mild + Moderate
DPB1*03:01	0.65 [0.4-1.0]	0.049	0.093	Mild + Moderate

[a] Odds ratio (OR) of being asymptomatic, i.e. OR>1 indicates that the allele is more frequent in asymptomatic individuals. CI: confidence interval.

[b] Allele frequency (AF) is based on the frequency of the allele in the CHGE European cohort 'All' analysis, which included the largest numbers of cases and controls.

[c] For each allele, the top-ranked result across three sets of symptomatic patients in the CHGE European sample is given.

HLA-wide meta-analysis

We then performed three meta-analyses, denoted M1, M2, M3 (**Figure 1B**), combining the results from our two independent cohorts with METAL [24]. The first used the strictest definitions for the groups: the HLA-WAS with the '0 symptoms' group of asymptomatic patients in the US prospective cohort and the HLA-WAS limited to patients with severe and critical disease only in the CHGE cohort (**Table S8**). The second meta-analysis combined the HLA-WAS with the 'Max 1 day' definition of asymptomatic patients for the US prospective cohort (0 symptoms or 1 symptom for 1 day) with the HLA-WAS with all symptomatic cases from the CHGE (**Table S9**). The final meta-analysis used the results for the asymptomatic and symptomatic groups most closely resembling those of the study by Augusto, Murdolo & Chatzileontiadou et al. (**Table S10**). The meta-analyses detected no statistically significant associations (at a corrected threshold of p<0.00047) between HLA alleles and asymptomatic SARS-CoV-2 infection (**Table 3**, **Tables S8-10**). The top-ranked HLA allele was HLA-B*40:02 (p-value = 0.0008), for which enrichment was observed in asymptomatic individuals relative to symptomatic individuals in both cohorts and in the meta-analysis based on the strictest definitions.

Table 3: Top-ranked alleles in the meta-analyses and corresponding results in the US prospective and CHGE cohorts.

Allele	Meta-analysis			US Prospective Cohort[b]		CHGE Cohort[b]	
	Meta-analysis number	OR [95% CI][a]	p value	OR [95% CI][a]	p value	OR [95% CI][a]	p value
B*40:02	M1	3.51 [1.7-7.3]	0.0008	4.05 [0.7-24.6]	0.128	3.42 [1.5-7.7]	0.005
DPB1*01:01	M2	0.43 [0.3-0.7]	0.0015	0.43 [0.2-1.0]	0.058	0.43 [0.2-0.8]	0.010

DQA1*01:02	M3	1.41 [1.1-1.8]	0.007	1.31 [0.9-1.8]	0.119	1.54 [1.1-2.2]	0.022
A*23:01	M2	2.22 [1.2-4.0]	0.007	2.14 [0.7-6.6]	0.186	2.25 [1.1-4.4]	0.019
DQB1*06:02	M3	1.46 [1.1-2.0]	0.013	1.52 [1.1-2.2]	0.025	1.33 [0.8-2.2]	0.276
C*03:03	M1	0.52 [0.3-0.9]	0.015	0.48 [0.2-1.2]	0.132	0.54 [0.3-1.0]	0.055
B*49:01	M3	1.96 [1.1-3.4]	0.019	1.29 [0.4-3.9]	0.657	2.26 [1.2-4.3]	0.014
B*07:02	M3	1.42 [1.1-1.9]	0.021	1.58 [1.1-2.3]	0.016	1.16 [0.7-1.9]	0.554
DRB1*15:01	M3	1.38 [1.0-1.9]	0.037	1.42 [1-2.1]	0.075	1.32 [0.8-2.2]	0.264

[a] Odds ratio (OR) of being asymptomatic, i.e. OR>1 indicates that the allele is more frequent in asymptomatic individuals. CI: confidence interval.

[b] For each allele, ORs and p values obtained in the US prospective and CHGE cohorts with asymptomatic or controls definitions used in the corresponding meta-analysis are given.

Lack of replication for HLA-B*15:01

An analysis focusing on HLA-B*15:01 did not replicate the association between HLA-B*15:01 and asymptomatic SARS-CoV-2 infection (**Figure 2A-C**) despite being well powered (>95%) to detect an effect similar to that reported by Augusto, Murdolo & Chatzileontiadou et al. (OR of 2.40 for enrichment in asymptomatic vs. symptomatic patients, $p=5.67x10^{-5}$) (**Figure S3**). We further estimated the frequency of HLA-B*15:01 in various groups of patients of the CHGE consortium, including children with SARS-CoV-2 infection complicated by multisystem inflammatory syndrome (classified as MIS-C) and individuals with high levels of exposure who never tested positive (classified as 'resistors') [12,27]. This frequency ranged from 2.4% in asymptomatic individuals to 6.0% in resistors (**Figure 2C-D**). We also looked at individuals from non-European genetic ancestries. Similarly, we found no difference in frequency between asymptomatic and symptomatic individuals (**Figure 2E and Table S11**). Overall, no enrichment in the HLA-B*15:01 allele was observed among asymptomatic individuals in our US population-based prospective cohort, or in the international CHGE cohort.

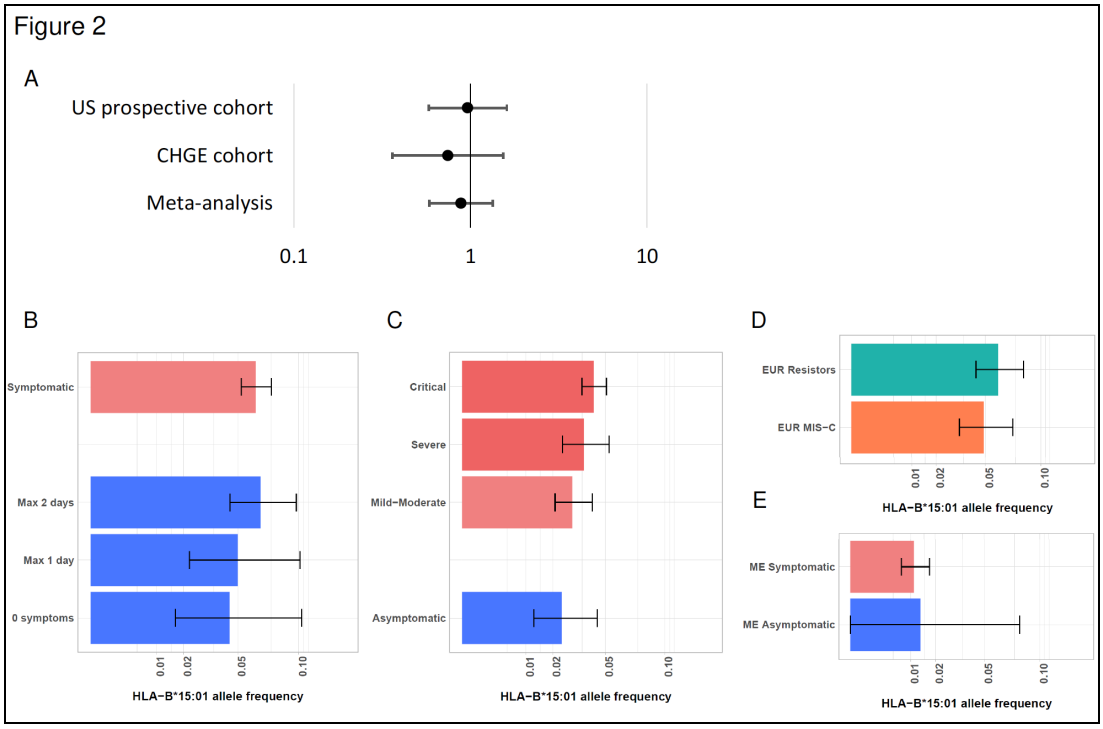

Figure 2: HLA-B*15:01 is not enriched in asymptomatic cases.
A: Odds Ratio (OR) and 95% confidence intervals (CI) for the association of HLA-B*15:01 with asymptomatic SARS-CoV-2 infection in both cohorts and in the meta-analysis.
B: Allele frequency and 95% confidence intervals in the US prospective cohort subgroups.
C: Allele frequency and 95% CI in the CHGE European sample.
D: Allele frequency and 95% CI in individuals highly exposed to SARS-CoV-2 who never tested positive ('Resistors', n=291) and children with SARS-CoV-2 infection complicated by multisystem inflammatory syndrome ('MIS-C', n=235) from the European CHGE sample.
E: Allele frequency and 95% CI in Middle Eastern (ME) individuals from the CHGE cohort (Symptomatic, n=895; Asymptomatic, n=37).

Symptoms and serology for participants with HLA-B*15:01 in the SARS-CoV-2 Human Challenge Characterisation Study

The mechanism proposed as an explanation for the association between HLA-B*15:01 and asymptomatic SARS-CoV-2 infection was pre-existing immunity, probably due to prior infection with OC43-CoV or HKU1-CoV [15]. Unfortunately, no serological data were available for the HLA-B*15:01 carriers in the US prospective and the CHGE cohorts. We tested the hypothesis that the lack of association in our study was due to an absence of prior infection with OC43-CoV or HKU1-CoV by examining the data for the SARS-CoV-2 Human Challenge Characterisation Study (ClinicalTrials.gov identifier NCT04865237; funder, UK Vaccine Taskforce), in which 34 participants seronegative to spike protein were challenged with D614G-containing pre-Alpha SARS-CoV-2, of whom 33 consented for genetic analysis [17]. Serological data, history of prior

infections with other coronaviruses and genetic data were available, together with infection status and data concerning the recorded symptoms. HLA alleles were called with HLA*LA from whole-genome sequences obtained from the participants. Three of the 17 infected participants (positive test result) carried an HLA-B*15:01 allele, as well as three of the 16 who stayed uninfected. Only one of the 17 infected participants was fully asymptomatic and this participant did not carry the HLA-B*15:01 allele. The three infected participants with an HLA-B*15:01 allele were symptomatic (**Figure 3**), despite evidence of prior exposure to OC43-CoV and HKU1-CoV (**Figure S4**). Thus, prior exposure to a coronavirus did not prevent the HLA-B*15:01 carriers from developing symptoms following SARS-CoV-2 infection.

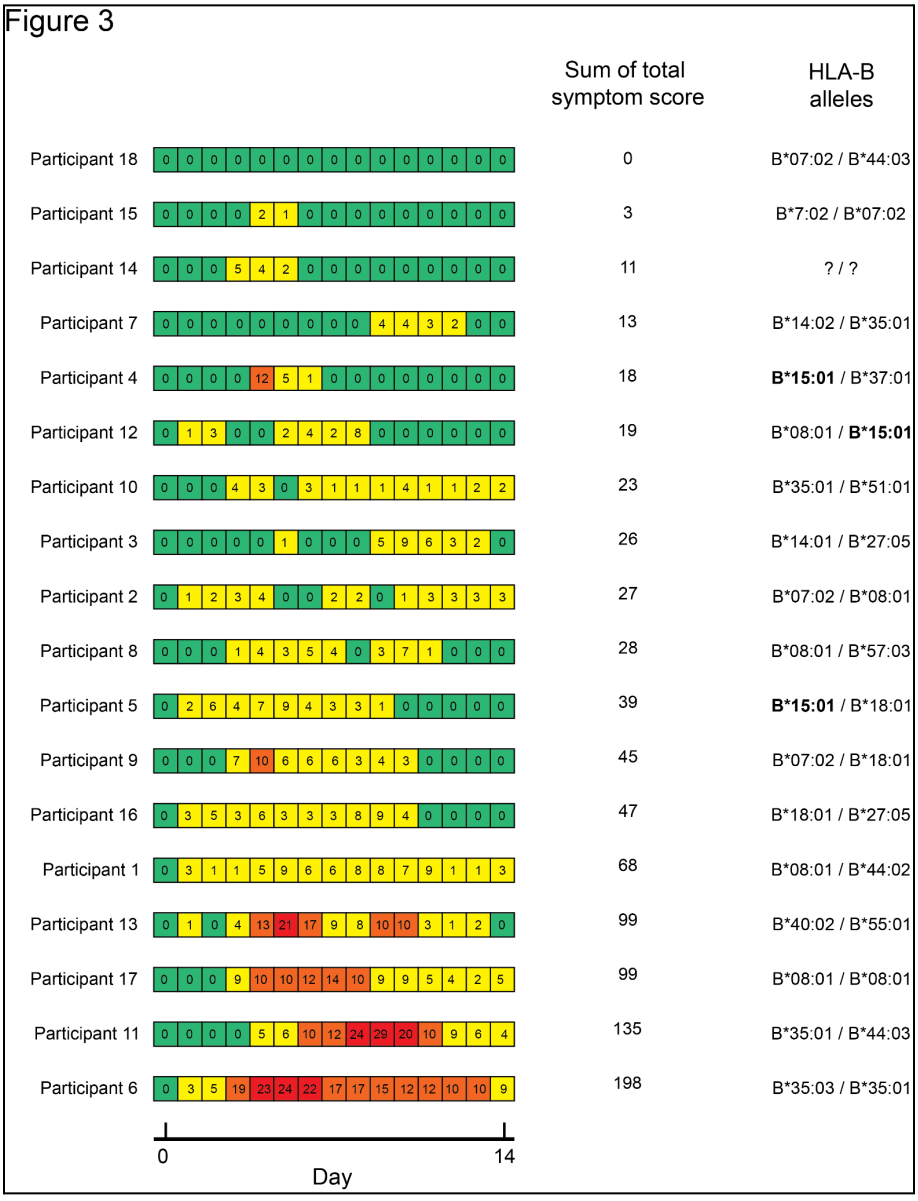

Figure 3: HLA-B*15:01 in the SARS-CoV-2 Human Challenge Characterisation Study.

Symptoms and HLA-B genotypes for 18 infected participants. Daily total symptom score was calculated using self-reported symptom diaries three times daily. Daily total symptom scores are displayed in the heatmap, ranging from green (no symptoms) to red (highest symptom score). The heatmap is derived from figure 2 in Zhou J. et al, *Lancet Microbe* (2023).

Discussion

Our analyses identified no associations between classical HLA alleles and asymptomatic SARS-CoV-2 infection. In particular, we did not replicate the previously reported association between HLA-B*15:01 and asymptomatic SARS-CoV-2 infection. Another recent study in a Spanish cohort found no associations between classical HLA alleles and asymptomatic SARS-CoV-2 infection [28]. One possible explanation for the difference in results regarding HLA-B*15:01 is that the studies analyzed different groups of individuals living in different environments. However, the US prospective cohort we analyzed has many features in common with the cohort analyzed by Augusto, Murdolo & Chatzileontiadou et al.: specifically, the participants were from the US, with a slight bias towards women, the phenotype was assessed on the basis of self-reported surveys at multiple time points during the pandemic before summer 2021 (before the SARS-CoV-2 Delta variant became dominant in the US [29]). The percentage of individuals self-reporting asymptomatic infection were similar between the two, as were the rates of each symptom. Alternatively, the difference in results may reflect differences in the handling of potential population stratification. Augusto, Murdolo & Chatzileontiadou et al. did not consider population structure in their study on bone marrow donors, probably because no genetic information outside of the HLA region was available, whereas we accounted for population structure by restricting our analysis to those of European ancestry and including the first five principal components as covariates in our regression model. The highly polymorphic nature of the HLA region and the differences in allele frequencies between human sub-populations contribute to a high risk of false-positive results in association analyses. The frequency of HLA-B*15:01 is known to vary across continents, between continental populations within the US (**Figure S5A**) and even between European countries (**Figure S5B**). Population stratification may, thus, have played a confounding role in the study by Augusto, Murdolo & Chatzileontiadou et al.

Overall, the absence of an association between classical HLA alleles and asymptomatic SARS-CoV-2 infection is consistent with the modest impact of HLA variation on severe or critical COVID-19 [30]. Most genetic and immunological studies of severe or critical COVID-19 pneumonia in unvaccinated individuals have implicated type I IFNs, suggesting that intrinsic and innate immunity play a more crucial role than adaptive immunity in the early response to SARS-CoV-2. Pre-existing immunity due to prior infections with common cold coronaviruses may help to prevent the development of symptoms following SARS-CoV-2 infection, but our

results suggest that either (i) pre-existing CD4 and CD8 T-cell immunity may not play an important role, or (ii) pre-existing immunity is not stronger for individuals with a particular HLA allele than for those with any other HLA allele. This result is also consistent with the absence of any strong association between HLA alleles and clinical outcomes during the acute phase for the other primary viral infections studied to date [31–33]. By contrast, HLA alleles have been associated with multiple clinical or laboratory outcomes during chronic infections, including viral (e.g., HIV, HBV, HCV), mycobacterial (e.g., leprosy) and protozoan infections [33–36]. HLA alleles are also known to be associated with adaptive immune responses to vaccinations [13,37,38]. Our findings suggest that memory T-cell immunity to seasonal coronaviruses does not strongly influence the outcome of SARS-CoV-2 infection in unvaccinated individuals.

Supplemental information

Supplemental information includes five figures and eleven tables.

Declaration of interests

E.T.C., K.M.S.B., and A.B. are employees of Helix.

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Web resources

HLA alleles distribution across populations:

Allele frequency Net Database: https://github.com/slowkow/allelefrequencies

1000 Genomes Project: http://ftp.1000genomes.ebi.ac.uk/vol1/ftp/data_collections/HLA_types/

Data availability

Data supporting the findings of this study are available within the manuscript and supplemental files. The whole-genome sequencing data of anonymized patients recruited through the National Institutes of Health (NIH) and sequenced at the National Institute of Allergy and Infectious Diseases (NIAID) through the Uniformed Services University of the Health Sciences (USUHS)/the American Genome Center (TAGC) are available under dbGaP submission phs002245.v1. Other patients were not consented to share the raw WES/WGS data files beyond the research and clinical teams.

Author contributions

AM, A Cobat, and AB performed computational analysis. AM, ETC, IN, EB, RT, KMSB, YZ, INB, MK, A Catchpole, JBL, CLD, VSS, A Cobat and AB performed or supervised experiments, generated and analyzed data, and contributed to the manuscript by providing figures and tables. SGT, ANS, JG, CB, GG, FT, PH, SYZ, QZ, CC, JF, JJG, VSS and the consortium collaborators

evaluated and recruited patients and /or controls. AM, LA, JLC, A Cobat, and AB wrote the manuscript. CC, JJG, LA, JLC, A Cobat, and AB supervised the project. All authors edited the manuscript. All authors read and approved the final manuscript.

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