

How could our genetics impact COVID-19 vaccine response?

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Abstract

Introduction: The COVID-19 pandemic, caused by the SARS-CoV-2 virus, has posed unprecedented global health challenges since its emergence in December 2019. The rapid availability of vaccines has been estimated to save millions of lives, but there is variation in how individuals respond to vaccines, influencing their effectiveness at an individual, and population level.

Areas covered: This review focuses on human genetic factors influencing the immune response and effectiveness of vaccines, highlighting the importance of associations across the HLA locus. Genome-Wide Association Studies (GWAS) and other genetic association analyses have identified statistically significant associations between specific HLA alleles including HLA-DRB1*13, DBQ1*06, and A*03 impacting antibody responses and the risk of breakthrough infections post-vaccination. Relationships between these associations and potential mechanisms and links with risks of natural infection or disease are explored, and this review concludes by emphasizing how understanding the mechanisms of these genetic determinants may inform the development of tailored vaccination strategies.

Expert opinion: Although complex, we believe these findings from the SARS-CoV2 pandemic offer a unique opportunity to understand the relationships between HLA and infection and vaccine response, with a goal of optimizing individual protection against COVID-19 in the ongoing pandemic, and possibly influencing wider vaccine development in the future.

Key words: COVID-19, vaccine, SARS-CoV-2, immune response, human genetics, HLA, GWAS

1. Introduction

In December 2019, a cluster of pneumonia cases with an unknown cause emerged, which was rapidly identified as being caused by a novel beta coronavirus [1], subsequently named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). The disease resulting from infection with this virus was defined as Coronavirus Disease 2019, or COVID-19. SARS-CoV-2 spreads directly through droplets and human-to-human transmission as well as indirectly through exposure to airborne contamination and infected objects [2]. Symptoms of COVID-19 develop up to 14 days following exposure. Patients usually have symptoms of high fever, dry cough, and dyspnea. The majority also have fatigue, myalgia, headache, weakness, nausea, rhinorrhea, with smaller numbers reporting anosmia or ageusia [3,4]. However, about 40–45% of the patients are known to be asymptomatic [5]. Numerous complications have been reported secondary to COVID-19 including pneumonia, acute respiratory distress syndrome (ARDS), liver injury, cardiovascular disease, thrombosis, multi-organ failure, and death [6–10].

The emerging COVID-19 pandemic necessitated a global response, which in many ways is ongoing. The virus has evolved, leading to the emergence of new variants, some of which have mutations that render them less susceptible to immunity developed from prior infections or vaccinations [3]. The rapid development and distribution of vaccines have been monumental in curbing the spread [11]. It is clear that individuals have significant differences in how they respond to both natural infection and vaccination. Understanding the relationships between such differential susceptibility to infection, risk of adverse outcomes, and vaccine responses could provide significant insights into long-term management and prevention strategies not only for COVID-19 but also for other infections of public health importance.

This review aims to summarize our understanding of how human genetics influences both immunological and clinical response to COVID-19 vaccination, and how this relates to the risk of natural COVID-19 disease, and how we may be able to use this information to improve vaccine development and future public health decision-making.

2. The SARS-CoV-2 Virus

SARS-CoV-2 is a single stranded, positive sense RNA virus. It has a genome size of 29.9 kb, enclosed by an envelope membrane and the spike protein, typical of the coronavirus group [12–14]. The genome of SARS-CoV-2 (Figure 1) consists of a 5' leader sequence (L) followed by two open reading frames (ORF1a and ORF1b) which initiate the viral genome replication and transcription, then four structural genes called spike, envelope, membrane, and nucleocapsid (S, E, M, and N), and a 3' untranslated region (UTR) [15]. All the different proteins produced by the virus are separated by the transcription regulatory site (TRS), which is important for virus replication [16]. Structural proteins and accessory genes are coded by transcripts of sub-genomic mRNAs, which all join with the common leader sequence [16,17].

As the virus replicates, it can undergo genetic changes, leading to mutations. Some of these mutations can result in the formation of new variants. Estimates from 2022 demonstrate that 2.7% of the analyzed SARS-CoV-2 genetic sequences exhibit signs of recombinant lineages, which could prospectively impact the transmissibility or virulence of the virus [18]. The continuous evolution of SARS-CoV-2, through mutations and recombination events, has led to the emergence of numerous variants [19]. Some of these variants have been classified as Variants of Concern (VOC), which have shown increased transmissibility or resistance to neutralizing antibodies [20]. The four representative VOCs include the Alpha, Beta, Delta, and Omicron variants [21]. Each of these variants possesses distinct genetic mutations and have demonstrated varying degrees of transmissibility, disease severity, and vaccine efficacy [22–26].

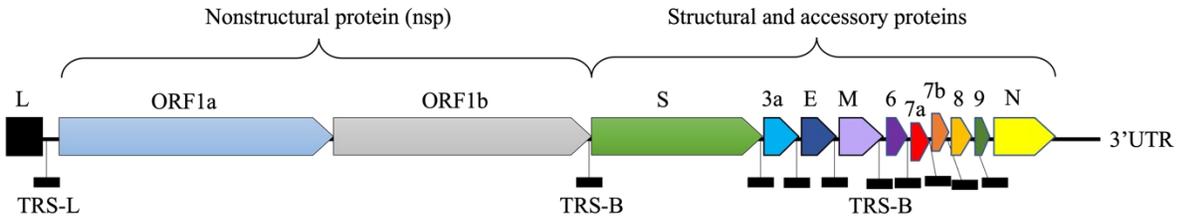


Figure 1. Genomic structure of SARS-CoV-2. Representation of mRNA has a 5' leader sequence (L), poly-A tail at 3' end, and 5' and 3' UTR. It consists of ORF1a, ORF1b, Spike (S), ORF3a, Envelope (E), Membrane (M), ORF6, ORF7a, ORF7b, ORF8, ORF9, Nucleocapsid (N), and a 3'UTR. The various proteins generated by the virus are distinguished by the transcription regulatory site (TRS) [27].

3. Vaccines for COVID-19

Several types of vaccines have been developed for COVID-19, encompassing inactivated, viral vectored, mRNA, DNA, and protein-based vaccines (Table 1), which are all designed to elicit an immune response against the SARS-CoV-2 S protein or its critical receptor-binding domain (RBD), thus inducing protection against COVID-19 [36]. These vaccines aim to induce an immune response, marked by the production of neutralizing antibodies capable of blocking virus entry into human cells and the activation of T-cell responses to eradicate infected cells (Figure 2). The primary vaccines that have been administered widely to the public and thus have been a significant focus of research studies to date include the BNT162b2 vaccine (Pfizer-BioNTech) and the ChAdOx1 nCoV-19 vaccine (Oxford-AstraZeneca) [29,31].

The ChAdOx1 vaccine, developed by the University of Oxford in collaboration with AstraZeneca, is a viral vectored vaccine. The ChAdOx1 vaccine utilized a genetically modified chimpanzee adenovirus, rendered nonpathogenic to humans. This adenoviral vector is engineered to carry a genetic sequence encoding the S protein found on the surface of the SARS-CoV-2 virus. Upon administration, the vaccine facilitates the cellular synthesis of S, acting as an antigenic stimulus that elicits adaptive immune responses. The ChAdOx1 nCoV-19 vaccine induces the expansion of CD4+ and CD8+ T cells against specific peptide epitopes of S. Consequently, upon subsequent exposure to the natural SARS-CoV-2 virus, the host's immune system is adeptly equipped to identify and neutralize the pathogen, mitigating the risk of severe clinical manifestations [37,38]. The ChAdOx1 vaccine is recognized to induce more potent cellular immune responses but weaker antibody reactions compared to mRNA vaccines [39]. The combined efficacy of full vaccination of ChAdOx1 against SARS-CoV-2 was 72.8% in preventing symptomatic infection, 94% in preventing hospitalization, and 97.2% in preventing severe infection [40].

BNT162b2, a mRNA vaccine, utilizes a specific segment of the SARS-CoV-2 virus' mRNA, which encodes directives for host cells to synthesize the virus's S protein. Upon its expression, the immune system is triggered to recognize it as an exogenous entity, instigating the generation of potent antibodies and the activation of T lymphocytes. Empirical investigations from the United States and Germany have ascertained that a dual-dose regimen of BNT162b2 induces elevated titers of SARS-CoV-2 neutralizing antibodies, accompanied by potent CD8+ and T helper type 1 (TH1) CD4+ T cell immunogenicity [41]. The efficacy of BNT162b2 was approximated at 95% against COVID-19 for individuals aged 16 and above [42]. A recent study has emphasized the importance of antibody titers in predicting vaccine efficacy, although with some unexplained heterogeneity [40]. These findings highlight that despite the obvious effectiveness of vaccination, there remains variation in how individuals may respond to, and be ultimately protected against vaccination.

Classification:
General

Early research into COVID-19 vaccine responses highlighted the role of variables including age, sex, immune history, obesity, and underlying health conditions in variance in response to vaccination [43,44]. There has long been a suspicion that human genetics can influence vaccine immune responses, in a manner similar to natural infection, but the extent to which this applies to COVID-19 vaccination, or the clinical relevance of such variation, is only recently becoming apparent. It stands to reason that if a vaccine antigen is protective against disease, as has been recognized for SARS-CoV-2 and COVID-19, then measuring responses against such conserved epitopes should provide a glimpse into the immune responses required for an effective immune response [45–47]. Studying COVID-19 vaccines should be particularly effective in this regard, given the wealth of vaccine data available, links between vaccine dosing, immune measures and vaccine effectiveness, and the simple nature of the vaccine antigen (Table 2).

Vaccine type	Advantages	Disadvantages	Example Licensed Vaccine	Comparative Efficacy
Inactivated, killed virus	Safety	Requires multiple doses; May require additional adjuvants; Shorter duration of protection; High cost; Reduced cell-mediated immunity	CoronaVac [28]	A study of 10.2 million individuals between 2 February and 1 May 2021 showed that the Sinovac vaccine provided 65.9% efficacy against COVID-19, 87.5% in averting hospitalizations, reducing ICU admissions, and 80.5% in averting COVID-19-related death [28].
Viral vectored	Considered as safe as vector agent; High cell-mediated immunity	Rare risks of thromboembolic disease; Antibody responses lower than mRNA and protein-based vaccine	ChAdOx1 nCoV-19 vaccine (AZD1222) [29]	Between 23 April to 4 November 2020, 11,639 individuals were enrolled into a phase 2/3 trial. 7,548 in the UK and 4,091 in Brazil. Preliminary primary efficacy analysis showed an overall efficacy rate of 70.4% in participants who were administered two doses, and a higher efficacy of 90.0% in those who were administered initially and then a standard dose [29].
			Ad26.COV2.S Vaccine [30]	Between 21 September to 22 January 2021, 19,630 individuals who received the vaccine and another 19,691 participants who received a placebo demonstrated effectiveness estimated from moderate to severe-critical COVID-19, the vaccine was 83.5% [30].
mRNA vaccine	Safe; High immunogenicity	Requirement for cold chain transport, rare risks of cardiac side effects	BNT162b2 mRNA Covid-19 Vaccine [31]	A global trial including 43,548 individuals between November 2020 and January 2021, including 21,728 given the vaccine, and 21,728 given a placebo. The primary endpoint of preventing COVID-19 to be 95% [31].
			mRNA-1273 SARS-CoV-2 Vaccine [32]	30,420 participants from the United States were assigned to two groups to receive either the vaccine or a placebo. The first dose was administered between 27 July and 23 October 2020. The vaccine showed an efficacy of 94.1% in preventing COVID-19 [32].
DNA vaccine	Safe; High stability	Lower immunogenicity; Mutations might be developed upon administration	ZyCoV-D [33]	From 16 January to 23 June 2021, 13,852 individuals in India were enrolled and randomized to receive either the ZyCoV-D vaccine and 13,852 individuals received a placebo. The primary endpoint was the prevention of COVID-19 [33].

				effectiveness of the ZyCoV-D vaccine [33].
Protein-based	Antibody responses 100 times greater than existing mRNA vaccines; More durable immune responses against VOCs in non-human primates; May be useful as a once-yearly booster vaccine, including in infants	Challenging storage conditions; High cost; The vaccine's efficacy and safety in humans are yet to be determined	DCFHP-alum (a ferritin-based protein nanoparticle vaccine) [34]	Assessed by immunization studies

Table 1. Comparative analysis of licensed COVID-19 vaccines.

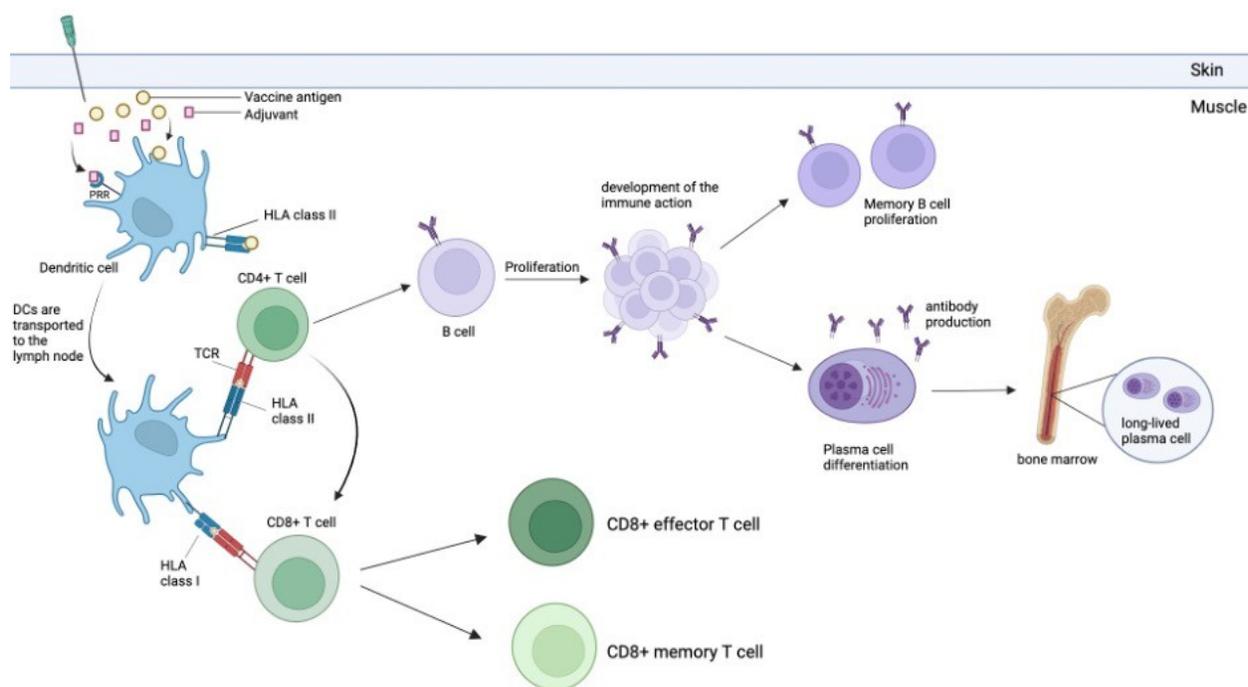


Figure 2. Proposed mechanism of vaccine-induced immune responses against any generic vaccine type. Upon administration, the vaccine is introduced by injection into myocytes, where the vaccine antigen is subsequently internalized by antigen-presenting cells (APCs). Adjuvants within the vaccine formulation are identified by pattern recognition receptors (PRRs) on these DCs and other innate immune cells that in turn secrete specific cytokines and present digested, internalised antigens via Human Leukocyte Antigen (HLA) molecules. Post internalization, DCs migrate to the lymph nodes. Antigens presented on HLA molecules on DCs activate T lymphocytes through T cell receptors (TCRs). Specifically, antigens presented on HLA class I molecules activate CD8+ T cells, and those on HLA class II molecules stimulate CD4+ T cells. Activated CD4+ T cells subsequently facilitate the activation of B lymphocytes, promoting their maturation within the lymph node. This maturation process enhances the affinity of antibodies (Abs) produced by these B cells. Differentiated plasma cells secrete antibodies specifically tailored against the vaccine antigen, while memory B cells are developed to provide long-term

immunological memory. Simultaneously, long-lived plasma cells are established within the bone marrow, ensuring a sustained antibody response over an extended duration. Alongside this humoral response, the induction of CD8+ memory T cells occurs. Figure is adapted from [35] and created using BioRender <https://www.biorender.com/>.

4. The impact of human genetic variation on SARS-CoV-2 vaccination

The Genome-Wide Association Study (GWAS) format has proven itself to be a powerful tool in identifying genetic factors that may influence biological traits [40,55]. Briefly, GWAS involves determining genetic variation at single nucleotide variants (SNVs) across the genome in large numbers of individuals who are defined either as cases or controls, or in whom a quantitative trait is measured [56]. SNVs can be determined using either array typing or increasingly next-generation sequencing is used. Subsequently, ‘missing’ SNVs can be statistically imputed using large sets of sequenced reference individuals to often provide tens of millions of variants across the genome for all individuals. Logistic or linear regression can then be performed for all SNVs testing for association between each individual SNV and the biological trait of interest. Careful adjustment for population structure, relatedness, and other potential confounding effects should be incorporated into these association models, before looking for loci that are associated with surrounding SNVs in linkage disequilibrium. Due to the large number of tests performed, highly stringent statistical thresholds (P-values $<5 \times 10^{-8}$) are generally required to indicate a true positive association. Furthermore, replication in an independent dataset is often necessary to truly validate these findings followed by functional validation where possible.

The first large-scale GWAS of SARS-CoV-2 vaccine responses examined data from 1,076 individuals. The participants, with a median age of 37, comprised 53.2% females and 46.8% males and were part of the ChAdOx1 nCov-19 vaccine efficacy trials in the United Kingdom. This study identified a genomic association between the HLA-DQB1*06 allele and increased antibody responses against the SARS-CoV-2 spike protein. This association was then replicated in an independent set of cohorts including 1,677 vaccine recipients who had received both the ChAdOx1 vaccine and the mRNA Pfizer-BioNTech vaccine, demonstrating that this effect was likely antigen-specific, rather than dependent on the formulation of the vaccine. The effect of HLA-DQB1*06 was shown to be persistent over time, as long as participants were being followed up in the original ChAdOx1 trials [29]. Of greatest importance, however, individuals with the HLA-DQB1*06 alleles demonstrated a reduced propensity for PCR-validated breakthrough infections during both the ancestral SARS-CoV-2 viral phase and Alpha variant in comparison to those lacking this specific allele.

This is the first time that a study has identified a genetic variant influencing both immunogenicity and effectiveness of a vaccine, benefitted by the sheer scale of vaccine studies available for COVID-19, and the uniqueness of the pandemic situation where incidence of disease was inevitable. The effectiveness signal was detected with only 112 cases of breakthrough infection very early in the COVID-19 pandemic, and therefore there is a possibility that this particular signal is variant-specific. Functional evidence for the HLA-DQB1*06 association with immunogenicity was provided by the identification of augmented spike-specific memory B cell activity and T-cell proliferation observed in HLA-DQB1*06 allele carriers at 84 days post-vaccination. The findings underscore the pivotal role of HLA type in modulating the antibody response to the COVID-19 vaccine and the associated risk of breakthrough infections, which provides compelling evidence on the importance of genetic factors in vaccine efficacy [48].

An association across the HLA region was also observed in an independent cohort in Italy. In a study of 873 individuals who received two doses of the BNT162b2 anti-SARS-CoV-2 vaccine, tests of association between genetic variants and post-vaccination IgG levels revealed a significant correlation with the HLA locus [49]. The median age of the cohort was 48 years, with a predominantly female demographic

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(82.7%). In contrast to the study in ChAdOx1, the discovery analysis was undertaken using responses against the Pfizer-BioNTech vaccine rather than ChAdOx1. The authors found the strongest association across the class I HLA region, and particularly HLA-A*03:01. Furthermore, the authors did identify an association with HLA-DQB1*06:01, which appeared independent of the class I signal, but was associated with a reduced antibody response. Overall, HLA-DQB1*06 was not significantly associated with responses in their analysis, although HLA-DQB1*06:04 was marginally associated with an increased response. Intriguingly, the current version of the analysis does not list adjustment for population structure in their HLA association analysis, and their discovery signal has not been replicated. However, it is noteworthy that HLA-A*03:01 has also been associated with adverse reactions against the Pfizer vaccine [57].

Another small study in Japan, including 100 individuals with a composition of 32% males and 68% females, also found evidence of association with responses against Pfizer-BioNTech. In healthcare workers, they identified HLA-DQA1*03:03:01 to be associated with increased IgG after two doses, whereas HLA-DQB1*06:01:01 was again associated with reduced levels. Moreover, HLA-C*12:02:02, HLA-B*52:01:01, HLA-DQA1*03:02:01, and HLA-DPB1*02:01:02 were linked to providing protection against systemic symptoms. Although these studies independently support the observation of an HLA locus association, the exact causal allele remains unclear [50].

Another recent study conducted a range of genetic analyses within a cohort of 368,098 individuals from UK Biobank who were known to have received their vaccinations, and within which 194,371 participants had undergone antibody serology testing. The participants in the cross-sectional cohort who received one dose of the vaccine had a mean age of 67.27, with 55.8% being female and 44.2% being male. For those who had received two doses of the vaccine, the mean age was 71.22, with 58.1% being female and 41.9% being male. Together, the authors of this study found that the carriage of DQB1*06 alleles not only significantly correlated with a more robust antibody response but also had a non-significant dose dependent correlation between antibody response and COVID-19, supporting the possibility of its link to the risk of breakthrough COVID-19 infection. Mendelian Randomization was utilized to estimate the causal effect of vaccine-induced antibody presence on the occurrence of breakthrough COVID-19 cases, revealing a protective influence that reduces the risk of breakthrough infections by 16.84%–21.68% and severe COVID-19 cases by 46.44%–49.94%. Moreover, the antibody response from vaccination offers about a 20% defense against SARS-CoV-2 infection and a larger protection, roughly 50%, against severe COVID-19 consequences. There was found to be a more pronounced association following the first vaccine dose compared to the second, with the DQB1*06:04 subtype revealing a notably stronger correlation with vaccine-induced antibodies than other DQB1*06 alleles including DQB1*06:02. Moreover, the authors noted that DQA1*01:01 consistently acted as an antibody inhibitor post either vaccine dose. Furthermore, six new functional HLA alleles were identified that independently impact the antibody responses induced by the vaccine.

Emphasizing the unique value of UK Biobank, an independent research team has recently undertaken a more focussed fine-mapping of HLA associations with the same serology testing trait available. They carefully defined 54,066 individuals who had received one dose of vaccine, and 46,232 who had received two doses and used these as discovery and replication cohorts to identify the allele HLA-DRB1*13:02 as having the most significant protective role in preventing IgG seronegativity. They went on to speculate that it was a specific alteration at position 71 in the HLA-DRB1 protein that was responsible for driving this association [51]. Collectively, these studies reinforce the critical role of genetic variation in influencing both immunogenicity and effectiveness of COVID-19 vaccine responses, with all studies emphasizing the potential impact of multiple alleles, including those within the serological classes HLA-DQB1*06, DRB1*13, and A*03 [58], although the nature and implications of these associations remain unclear.

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HLA allele	Association with SARS-CoV-2 infection	Vaccine against with	Country of Cohorts
DQB1*06 [48]	Higher levels of RBD IgG 28 days following vaccination	ChAdOx1	United Kingdom
A*03:01 [49]	Higher T1(2 months) antibody levels after vaccination	BNT162b2	Italian
DQA1*03:03:01 [50]	Higher S IgG post-vaccination	BNT162b2	Japanese
DQB1*06:01:01:01 [50]	Slower decline in S IgG levels over time post-vaccination	BNT162b2	Japanese
C*12:02:02; B*52:01:01; DQA1*03:02:01; DPB1*02:01:02 [50]	Protection against systemic symptoms	BNT162b2	Japanese
HLA-DRB1*13:02 [51]	Exhibited the most significant protective role in preventing IgG seronegativity	ChAdOx1 (36.9%) BNT162b2 (13.2%) Unknown (49.9%)	United Kingdom
DRB1*12:01 [52]	Significantly associated with enhanced Spike antibody production	BNT162b2	Japanese
DRB1*07:01 [53]	Elevated antibody levels observed 30 days following the second vaccination dose	mRNA-1273	Spanish
A*33:03; B*58:01 [54]	Diminished antibody response following vaccination	BNT162b2	Italian

Table 12. Vaccine type associations identified with HLA alleles, with correlation to COVID-19 vaccine response and infection outcomes.

5. The HLA locus and the relevance to COVID-19 disease

Classification:
General

The HLA locus is a genomic region characterized by pronounced allelic variation which is integral to the adaptive immune response to pathogens [59]. Proteins transcribed from *HLA* genes display viral epitopes on the surface of infected cells, facilitating their detection by T lymphocytes [60]. *HLA* is a complex family of genes that are located within a wider major histocompatibility complex (MHC) in humans, located on the short arm of chromosome 6, specifically at the region 6p21.31 [61]. This region contains numerous genes related to the immune system, including *HLA*, and the high rates of polymorphism occur not only within the *HLA* genes but across the entire locus [62]. The HLA system is traditionally segmented into three regions (class I, II, and III), encompassing numerous loci associated with inflammatory reactions. HLA class I encompasses the classical, highly polymorphic genes (*HLA-A*, *HLA-B*, and *HLA-C*) as well as the less polymorphic, non-classical MHC class I (Ib) molecules *HLA-E*, *HLA-F*, and *HLA-G* [63], and the human MHC class I chain-related genes (*MICA* and *MICB*) [64]. *HLA-DP* (*HLA-DPA1*, *HLA-DPB1*), *DQ* (*HLA-DQA1*, *HLA-DQA2*, *HLA-DQB1*, *HLA-DQB2*), and *DR* (*HLA-DRA*, *HLA-DRB1*, *HLA-DRB2*, *HLA-DRB3*, *HLA-DRB4* and *HLA-DRB5*) genes, as well as other genes with less variability that play roles in antigen processing and presentation are found in the class II region. The class III region contains genes associated with immune-related functions such as inflammatory reactions, leukocyte development, and the complement cascade [65].

GWAS has identified more associations at the HLA locus with diverse diseases and traits than for any other locus in the human genome, highlighting the importance of this region for immune responses and disease susceptibility. Of particular note, there are multiple associations described between HLA alleles and infectious diseases including tuberculosis [66] and Typhoid fever [67], localizing predominantly to the class II locus. Furthermore, there are associations across the class II HLA locus identified with antibody responses against both naturally occurring infection such as Epstein–Barr Virus and vaccine-induced responses against tetanus, diphtheria, pertussis, and hepatitis B [68]. Indeed, specific HLA variants have been reported to be associated with either enhanced [52,53] or reduced [54] serological responses. It is therefore intuitive that associations have been identified between the HLA region and responses against SARS-CoV2 vaccination.

Associations with HLA have also been found in the most recent GWAS meta-analysis of COVID-19 disease susceptibility (Table 3). The implementation of GWAS for COVID-19 disease severity demonstrated notable agility, attributable to the established collaborative frameworks from prior GWAS endeavors and the employment of preexisting genotyped cohorts, including the UK Biobank, AncestryDNA, and 23andMe [69–73]. As such, these analyses predominantly included individuals who were unvaccinated at the time of disease, because these cases were recorded before vaccines had been introduced, and vaccine introduction was associated with significant reductions in the incidence of severe and critical COVID-19. The most recent meta-analysis update including 219,692 cases and over 3 million controls has highlighted numerous biological pathways as being linked to COVID-19 susceptibility. Three major biological pathways involved in susceptibility and severity have been identified including viral entry, airway defense through mucus, and type I interferon response. Fifty-one distinct genome-wide significant loci are recognized to date, with 30, 40, and 21 loci, respectively, associated with critical illness, hospitalization, and infection caused by SARS-CoV-2 [74]. These insights have already given rise to clinical interventions, such as the use of baricitinib following identification of the TYK2 associations, where subsequent trials have demonstrated efficacy in the treatment of COVID-19 pneumonitis [75]. Interestingly, despite the well-recognized bias in males presenting with severe and critical COVID-19 disease, no genetic basis for this difference (such as through variation on the X chromosome), has yet been identified. Furthermore, despite the increasing evidence of an association with COVID-19 severity being present across the HLA region, these have not yet been fully fine mapped to the same extent as for vaccine response [58]. There has, however, been a tranche of smaller candidate gene association or immunology studies that have identified HLA alleles to be associated with disease susceptibility or outcomes, rather than simply vaccine response.

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A recent study by Augusto et al. has provided compelling evidence pointing toward an HLA allele influencing an individual's susceptibility to SARS-CoV-2 infection. Augusto and colleagues hypothesized that specific HLA alleles might modulate the underlying pathways culminating in asymptomatic infection. The study included an impressive 29,947 individuals with high-resolution HLA genotyping data enrolled in a smartphone-based study to test this hypothesis. The final analysis focused on 1,428 unvaccinated individuals who self-identified as white and reported a positive test result for SARS-CoV-2 to identify HLA alleles associated with asymptomatic SARS-CoV-2 infection. The results discovered a correlation between the HLA-B*15:01 allele and asymptomatic infection. This association was consistent across two independent cohorts, underscoring its potential significance. The authors further proposed that HLA-DRB1*04:01 may enhance the effect of HLA-B*15:01 [76]. The authors delved deeper into the molecular mechanisms and found that T cells from individuals with the HLA-B*15:01 allele from pre-pandemic samples exhibited reactivity to an immunodominant peptide derived from the SARS-CoV-2 spike protein, denoted as NQKLIANQF, suggesting preexisting T cell immunity [77]. This observation is further substantiated by the structural analyses of the HLA-B*15:01-peptide complexes, revealing a remarkable similarity in the stabilization and presentation capabilities of peptides derived from both SARS-CoV-2 and seasonal coronaviruses HKU1-CoV and OC43-CoV [78]. Collectively, the association between HLA-B*15:01 and asymptomatic infection suggests that individuals carrying this allele may have a genetic advantage in clearing the virus without developing symptoms, which not only improves our understanding of the host-pathogen interaction dynamics but also paves the way for future research for therapeutic and prophylactic interventions. These results highlight the importance of HLA alleles, particularly class I, not only in playing a critical role in modulating immune responses to SARS-CoV-2 but also for class II alleles significantly influencing the efficacy of vaccine-induced immunity against COVID-19.

In an alternative study, Nguyen et al. found that individuals carrying HLA-B*46:01 may be linked with increased severity of infection. Through a comprehensive in silico analysis, including sequence alignment, evaluation of conserved peptides, predictions of MHC class I binding affinity, and generation of global HLA allele and haplotype frequencies, they found that HLA-B*46:01 had the fewest anticipated binding peptides for SARS-CoV-2, insinuating that bearers of this allele could be particularly susceptible to COVID-19 [79]. This observation aligns with earlier findings that this allele was demonstrated to be associated with increased severity in the earlier coronavirus species SARS-CoV1 [80], although the authors did not demonstrate the relevance in vivo. Conversely, HLA-B*15:03 was identified as an allele with a significant capacity to display highly conserved SARS-CoV-2 peptides shared among prevalent human coronaviruses, aligning independently with the genetic analysis by Augusto et al. above. This supports the conclusions of a cross-reactive T-cell-mediated immunity [81,82], possibly conferred by prior exposure to other human coronaviruses [83] could be pivotal in understanding diverse immune responses across individuals. Another immunodominant response linked to mild episodes of the disease has been hypothesized for HLA-B*07:02 binding the nucleocapsid protein sequence 105–113. This was again demonstrated to be mediated through CD8+ responses incurring high antiviral effectiveness, reemphasizing the importance of class I HLA diversity in differential protection against disease [84], although another study that has just been released questions the HLA-B*15:01 results highlighting how difficult it can be to replicate and confirm HLA association findings [85].

Several subsequent studies have proposed further relationships between HLA alleles and SARS-CoV-2 susceptibility. For instance, HLA-A*15 and HLA-B*08 have been identified as risk factors for SARS-CoV-2 infection due to a deficiency in immune-dominant virus-derived epitope peptides, leading to inadequate immune responses [86]. In contrast, alleles like HLA-A*02:01, HLA-DR*03:01, and HLA-Cw*15:02 have been linked to resistance against SARS infection [87]. Other alleles including HLA-B*51, B*18, and B*14 have shown varying correlations with COVID-19 incidence, with some showing positive and others negative associations [88]. In terms of disease severity, HLA-A*33 has been linked to protection against severe forms of COVID-19, whereas HLA-B*38 and HLA-C*6 have been correlated

with a heightened risk [89]. HLA-B*44 and HLA-C*01 have been found associated with inflammatory autoimmune diseases resulting from SARS-CoV-2 infection and inappropriate immunological reactions [87,90,91]. A recent investigation by Akcay et al. further revealed a notable correlation between HLA-B*49 and HLA-DRB1*14 with SARS-CoV-2 infection, while also identifying HLA-C*03 as an allele associated with increased mortality in COVID-19 patients [92,93]. As for all previous diseases with postulated HLA allele associations, many of these associations discovered in small numbers of individuals should be interpreted with caution until either large-scale GWAS is available to compare against or until a careful meta-analysis is undertaken to understand which alleles are reproducible and robust.

HLA allele	Association with COVID-19 disease susceptibility	Mechanistic Basis/ Causal Factors
HLA-B*15:01 [76]	A strong correlation with Asymptomatic infection, this effect may be enhanced by the presence of HLA-DRB1*04:01	Pre-pandemic T cells in individuals showed a response to a key SARS-CoV-2 spike protein peptide, NQKLIANQF, indicating pre-existing immunity
HLA-B*46:01 [79]	Associated with a higher severity of infection	Has the least predicted SARS-CoV-2 binding sites
HLA-B*15:03 [79]	With a significant capacity to display highly conserved SARS-CoV-2 peptides	Enable a cross-reactive T-cell-mediated immunity
HLA-B*07:02 [84]	Linked to mild episodes of disease and strong effectiveness against viruses	Nucleoprotein (NP) is a regular epitope for CD8+ responses
HLA-A*15; HLA-B*08 [86]	Identified as risk factors for SARS-CoV-2 infection	Attributable to a scarcity of immunodominant virus-derived epitope peptides, culminating in suboptimal immune responses
HLA-B*49; HLA-DRB1*14 [92]	Linked to increased transmission of disease	Individuals may exhibit an incapacity to display requisite viral epitopes for T-cell repertoire formation
HLA-C*03 [92]	Associated with increased mortality in COVID-19 patients	Expression of this allele on cells may protect against destruction by natural killer (NK) cells, potentially inhibiting NK cell activity

Table 3. A review of HLA allele correlations to COVID-19 susceptibility and infection outcomes.

6. Novel Techniques: Shaping the Future of Vaccine Development

Observations of SARS-CoV-2 undergoing rapid and extensive genetic mutations, combined with variations in the allelic diversity of HLA across populations, and differences in T cell epitopes, all

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highlight the opportunities for refining vaccine strategies not only for COVID-19, but potentially also other infectious pathogens [94]. Within the scientific exploration of COVID-19 vaccines, while empirical data analysis from clinical trials remains paramount, there exists a burgeoning interest in understanding how we can use our increasing understanding of HLA associations in vaccine design. Combining knowledge on B-cell and T-cell epitopes aligning precisely with SARS-CoV-2 proteins, alongside knowledge of certain HLA alleles, could aid in generating immune responses to counteract SARS-CoV-2 infection [95].

As a proof of concept, before results from the large-scale analyses presented here were known, studies have shown that vaccines formulated with a mixture of peptides, derived from multiple epitopes restrained by the commonly interrogated HLA-A*02 molecule, have been shown to elicit a pronounced CD8+ T cell reactivity specific to SARS-CoV-2 in experimental animals [96]. Furthermore, these vaccines have demonstrated a protective effect by reducing lung damage in mice [97]. Moreover, a prospective vaccine candidate for SARS-CoV-2, encompassing multiple epitopes for T-helper cells, B-cells, and cytotoxic T-cells interconnected by linkers and supplemented with an adjuvant, has been developed in silico. Its development was informed by an analysis of its interaction with the HLA-B*15:03 subtype. This designed vaccine displays encouraging results, suggesting its potential to elicit an immune response and is a compelling opportunity in light of the findings highlighted above for the related HLA-B*15:01 allele linked with asymptomatic disease, where HLA-B*15:03 is more common in Sub-Saharan Africa [98]. The intricate relationship between specific HLA alleles and immune responses could hold the key to optimizing vaccine efficacy and tailoring immunization strategies. Such investigations not only aim to enhance our understanding of the genetic underpinnings influencing vaccine-induced immunity but also aspire to inform and optimize the framework for upcoming vaccine designs.

While there is growing evidence that human genetic variation influences vaccine effectiveness, there is also evidence that it may concurrently drive the emergence of vaccine resistance. For example, in research led by Kimura et al., the L452Q mutation identified within the Lambda strain of SARS-CoV-2 was revealed to impart resistance to antiviral immune responses. As viruses evolve, they can develop mechanisms to evade the immune responses triggered by vaccines. This mutation is predicted to arise as a consequence of immune pressure mediated by the HLA-A*24 allele, enabling the virus to circumvent HLA-A*24-restricted cellular immunity. Consequently, the Lambda variant not only demonstrates increased infectivity but also exhibits resistance to the neutralizing antibodies produced in response to the BNT162b2 vaccine [99]. Such instances highlight the complex relationship between viral genetic evolution and vaccine effectiveness, underscoring the importance of ongoing research and vaccine development efforts incorporating genetic variation information from pathogens.

Conversely, our increased understanding of how human genetic factors influence vaccine efficacy could pave the way for the development of specific host-directed therapies to combat COVID-19 [100]. Creating such insights will undoubtedly require a deeper understanding of the relationship between vaccine immunogenicity and the risk of disease. However, considering the effectiveness of the monoclonal antibodies targeting IL-6 (e.g. tocilizumab [101]) in reducing the impact of the ‘cytokine storm’ in COVID-19 patients, it is reasonable to suggest that we could use insights from future genetic work to improve vaccine effectiveness. If, for example, we were able to identify the specific mechanisms underlying the HLA associations or if we found other non-HLA genetic associations correlating with vaccine immunogenicity and effectiveness, we may be able to upregulate specific biologic pathways using biologic therapy, thus ensuring greater protection against disease.

It is highly likely that as more information is gathered relating to the impact of human genetic variability and COVID-19 susceptibility and vaccine responsiveness, the amassed information may be used to inform the future spread and control of infectious diseases [102]. For example, a recent study by Malone et al. applied artificial intelligence (AI), including Monte Carlo simulations and digital twin simulations,

as well as machine learning algorithms like Support Vector Machines (SVMs) and binding affinity predictors, to forecast templates for designing comprehensive vaccines against SARS-CoV-2 [103]. By meticulously profiling the entire SARS-CoV-2 proteome across a diverse range of HLA alleles, the investigators identified epitope hotspots that could be pivotal in a vaccine formulation to ensure broad coverage across the global population. Epitope hotspots with substantial similarity to human proteins were excluded to minimize the risk of triggering unintended autoimmune reactions [103].

Furthermore, another study by Chu et al. [104] have pioneered the development of the TransMut framework, utilizing transformer-based models to predict peptide-HLA class interactions, a vital aspect of antigen presentation and T-cell recognition. Such interventions could enhance peptide vaccine design [105]. The authors also provided an automatically optimized mutated peptides (AOMP) program, which is claimed to expedite the identification of immunogenic peptides and refining mutated peptides for superior affinity with specific HLA alleles, ensuring the efficacy and safety of prospective vaccine candidates [106,107]. These studies highlight the transformative role of AI in deepening our understanding of the human genetic of COVID-19 and in shaping personalized vaccine strategies tailored to varied genetic profiles (Figure 3). This progress emphasizes AI's potential with the help of the study of genetics to streamline and enhance the vaccine design process in the future work, particularly in the realm of personalized medicine and neoantigen targeting. In essence, the confluence of genetics and new technologies promises a more informed and strategic approach to combating future outbreaks and optimizing individual health outcomes.

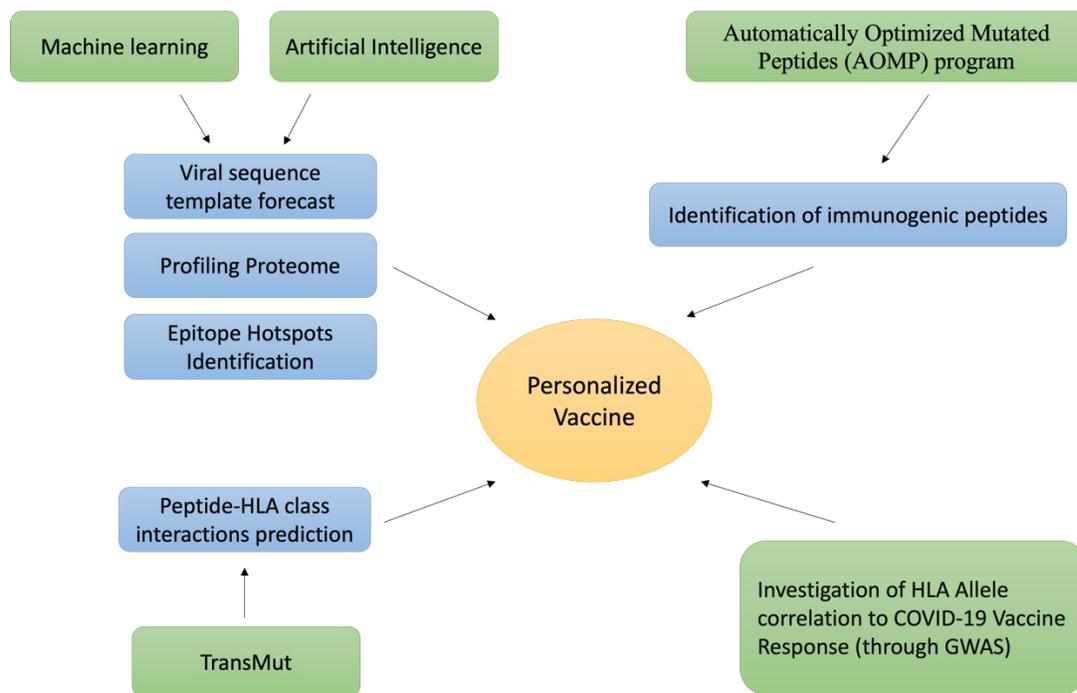


Figure 3. Potential novel techniques and consideration factors for the COVID-19 vaccine personalization.

7. Expert Opinion

It is increasingly apparent that human genetic variation impacts significantly on response to SARS-CoV2 vaccination and susceptibility to COVID-19 infection. These insights have only come about through the participation and inclusion of very large numbers of individuals in multiple research studies. On the one hand, these findings are at risk of being disregarded because the effect sizes of single genetic variants are

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small and so the clinical significance is questioned. However, the vast majority of genetic associations discovered with all biological traits are small, and we know through other diseases that, at a population level, these associations can be targeted therapeutically and result in significant improvements in outcomes. Furthermore, at an individual level, any avoidance of disease, where disease is genetically more likely than the next person, will be desirable. Findings at the HLA locus are unique. Compared to other genetic associations, the effect sizes are typically much larger. HLA associations are common among many disease types, yet the mechanisms responsible for these associations remain obscure. The findings for SARS-CoV2 vaccines and COVID-19 susceptibility are no different, yet their discovery offers, in our opinion, significant opportunities over and above those possible for other diseases that have been traditionally more studied, such as autoimmune disease.

Firstly, the sheer scale at which research has been undertaken trying to understand the molecular mechanisms of disease susceptibility and outcomes, and the variable effectiveness of vaccines, offers a plethora of cohorts from different ancestral populations, to study the associated genetic factors within. This is particularly important for HLA because of the recognized diversity stratified by ancestry, and it will only be through inclusion of greater diversity at larger sample sizes that discovery and validation of signals will truly be possible. Secondly, the comparatively simple nature of the SARS-CoV2 virus compared to other pathogens of global importance limits the number of antigens that are culprits for driving HLA associations with disease susceptibility, assuming that it is antigen processing and peptide presentation that are the disease mechanisms of relevance. The HLA associations with vaccination are simpler to dissect because only a single antigen, Spike, was delivered in the vast majority of cases. Therefore, it makes enormous sense to focus on bringing together as many vaccine cohorts as possible to understand the HLA associations with vaccine response in detail, before aligning these with disease susceptibility, to understand, the contribution of Spike, as opposed to other antigens, to disease. The final benefit of studying HLA associations with SARS-CoV2 specifically in the context of the global research response effort is the availability of vast amounts of immunological data in the public domain. This makes it simpler to move from genetic discovery to immunological mechanism elucidation, avoiding further excessive expenditure if experimental design can be informed through previous work.

Given these insights, the path to clinical translation seems clear. It is important for researchers to continue to present and disseminate their work publicly looking at the impact of genetics on vaccine response and disease susceptibility, particularly including individuals from diverse ancestral backgrounds, and preferably from large studies such as biobanks. For HLA associations, the findings from vaccine response should be prioritized to understand the population specificity of biological signals, likely confounding variables, and the link to spike antigen sequence that may, in turn, inform biological mechanism. The findings should then be compared against those available for disease susceptibility described in multiple ways, including asymptomatic infection (the most desired outcome), or severe disease.

Simultaneously, experiments should be designed to understand the molecular mechanisms underlying these observed associations, so that the method to overcome reduced vaccine response, or increased disease susceptibility, can be identified and pursued. Is it simply differential peptide presentation that drives these observed associations or is it some other feature such as cellular frequency, activation state, or *HLA* gene expression effect that should be manipulated to exert differential effect? Or is it even some other gene in the wider MHC locus that is responsible for these genetic associations as has been speculated for several other diseases. Ultimately, these findings could be significant, guiding more effective vaccination strategies across populations, integrating genetic with other environmental and lifestyle factors, to improve public health. Furthermore, these insights could enhance vaccine development through combinatorial antigen peptide inclusion, or varied adjuvant cocktails to target mechanisms of altered peptide binding or cellular immune responses, respectively, ensuring that future vaccines cater to a broader genetic diversity, thereby enhancing their effectiveness across different populations.

However, the practical implementation of these pathways into research and clinical practice translation faces multiple challenges. Statistical methods for understanding or fine-mapping HLA associations with biological traits need substantial development. Furthermore, the rapid mutation rate of the virus adds significant challenge because linking vaccine immune response to disease susceptibility or breakthrough infection becomes very difficult if the virus mutates away from a predominant antigen-specific presentation mechanism. Moreover, despite the benefits that having more data holds, the challenges of data handling and analysis accounting for population and study heterogeneity can be potentially show stopping. Therefore, we will certainly depend on continued algorithmic development to handle this data complexity in the future.

The next 5 to 10 years is almost certain to shift toward more personalized medical approaches, integrating genetic profiling into routine clinical practice for vaccine strategy development. This evolution will be dependent on AI and machine learning, capable of analyzing large-scale genetic datasets, uncovering patterns and correlations that might elude traditional *in silico* methods. These algorithms, leveraging their advanced analytical capabilities, can delve into complexities and subtleties in the data that conventional computational methods might overlook. Machine learning models could predict individual vaccine responses based on genetic and other clinical data, leading to optimized vaccine doses tailored to individual genetic profiles. SARS-CoV2 could indeed be the herald of the integration of such advanced technologies to improve the precision and efficiency of vaccine development and deployment, and the integration of genetic association informing more personalized immunization strategies, thus optimizing individual protection against SARS-CoV-2.

8. Conclusions

Altogether, there is growing and significant evidence that human genetics influences both immune responses against COVID-19 vaccines and susceptibility to severe disease. At present, the only consistent and robust signal for variable vaccine response and outcomes is limited to the HLA region. There is not yet good evidence for a single causal allele associated with these vaccine responses, although a signal between the *HLA-DR-HLA-DQ* is almost certain. Furthermore, in the absence of a formal analysis of the HLA region in the large disease GWAS, there is little evidence of an overlap in any alleles between vaccine response and disease susceptibility. Advancing the field will require a careful meta-analysis of the emerging studies to understand the reasons for underlying differences in association signals, which are observed frequently for diseases with associations across the HLA region. The observed variability in immunogenic outcomes across diverse populations underscores the multifaceted genetic architecture influencing vaccine efficacy [108]. These genetic nuances significantly influence vaccine responsiveness, highlighting the need for tailored immunization strategies. As SARS-CoV-2 continues to have a significant impact on public health [109], a comprehensive understanding of these genetic factors is crucial. Furthermore, the insights gleaned through their research could inform the development of new vaccines targeting multiple infections, paving the way for personalized immunization strategies, optimizing protection, and reducing disease susceptibility at the population and individual level.

Article highlights

- SARS-CoV2 led to the most significant pandemic of modern times.
- Vaccination against SARS-Cov2 was one of the most successful coordinated public health initiatives ever undertaken.
- Human genetic variation has been consistently linked with variable immunogenicity against diverse SARS-CoV2 vaccines.
- Genetic variation has also been associated with risk of breakthrough infection following vaccination, and COVID-19 susceptibility.
- Variation across the HLA, particularly DRB1*13, DBQ1*06, and A*03 have been shown to be important in vaccine response and disease risk post-vaccination.
- Further understanding mechanisms underlying these HLA associations require continued data generation and sharing.
- Sharing of data from diverse populations may be particularly informative.
- Future approaches involving Artificial Intelligence could help use these associations to inform future vaccine design.

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