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Review Article

An overview of HLA variants in COVID-19 vaccine-induced autoimmunity

Abdellatif Bouayad

Department of Immunology, Faculty of Medicine and Pharmacy of Oujda, Mohammed First University, Oujda, Morocco

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Abstract: COVID-19 vaccination, both in healthy individuals and those with comorbid medical disorders, has proven highly effective in mitigating critical disease progression and mortality rates. Nevertheless, although rare, induction of autoantibodies and new-onset autoimmune conditions in apparently healthy individuals receiving COVID-19 vaccination have been documented. These autoimmune phenomena can be broadly classified into organ-specific autoimmune disorders (e.g., subacute thyroiditis (SAT)) and systemic autoimmune disorders, with many being generally transient (e.g., vaccine-induced thrombotic thrombocytopenia (VITT)) and others causing chronic disability (e.g., systemic vasculitis). Recent studies have highlighted significant associations between COVID-19 vaccine-associated autoimmunity and human leukocyte antigen (HLA) loci. For example, HLA class I alleles such as HLA-B*35 and HLA-C*04 have been associated with COVID-19 vaccine-induced SAT, while HLA class II alleles, including HLA-DRB1*11:04, HLA-DQA1*05:01, HLA-DQB1*02:01, and HLA-DPB1*17:01, have been linked to VITT. This review synthesizes the reported associations between classical HLA loci and COVID-19 vaccine-induced autoimmunity, providing insights into potential mechanisms and clinical implications.

Keywords: Human leukocyte antigen, HLA class I, HLA class II, COVID-19 vaccines, autoimmunity, autoimmune diseases, autoantibodies

Introduction

Vaccination is a cornerstone of infectious disease control, with COVID-19 vaccines significantly reducing morbidity and mortality worldwide [1]. These vaccines utilize three principal technological platforms: replication-incompetent adenoviral vectors (e.g., Johnson & Johnson and AstraZeneca), messenger RNA (mRNA) (e.g., Moderna and Pfizer vaccines), and inactivated virus (e.g., Sinopharm and Sinovac).

While the efficacy and safety of COVID-19 vaccines are well documented, post-vaccination immune-related complications, including the development of autoimmune (AI) manifestations, have been reported in a small number of healthy individuals as well as in those with pre-existing AI conditions [2]. AI responses may range from the transient production of autoantibodies (AutoAbs) without clinical manifestations to an increased risk of developing various AI diseases, including alopecia areata, psoriasis, rheumatoid arthritis, autoimmune glomerulonephritis, and autoimmune hepatitis [3, 4].

The mechanisms underlying AutoAbs induction and AI phenomena in a small subset of individuals, as opposed to others, remain unclear. Since antigen presentation and T-cell activation are central to initiating autoantibody production [5] and tissue infiltration by autoreactive cytotoxic T lymphocytes (CTL) [6, 7], polymorphisms in human leukocyte antigen (HLA) molecules may partly explain inter-individual variation in vaccine responses. Across various ethnic populations, several investigations have documented associations between HLA alleles and vaccine-induced AI conditions, such as subacute thyroiditis (SAT) [8, 9], type 1 diabetes mellitus (T1DM) [10], and polymyalgia rheumatica (PMR) [11]. HLA variations have also been recognized as an important factor of COVID-19

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vaccine immunogenicity, influencing both protective adaptive immune reactions and systemic inflammatory adverse effects such as fever, chills, and fatigue [12-14]. In addition to HLA genetic predisposition, non-genetic factors such as older age [15], frailty [16], and comorbidities [17] may further modulate immune responses triggered by COVID-19 vaccines, thereby contributing to variability in the risk of developing AI phenomena.

This review synthesizes the reported associations between classical HLA loci and COVID-19 vaccine-induced autoimmunity, providing insights into potential mechanisms and clinical implications.

Overview of HLA genes and molecules

HLA gene loci fall into three main classes, each with distinct features. HLA class I region (HLA-I) includes three classical genes coding for HLA-I alpha (α)-chain (HLA-A, HLA-B, and HLA-C). HLA-I molecules acquire cytoplasmic peptides generated via the breakdown of intracellular proteins by the proteasome. The complex of transporter associated with protein processing (TAP) subsequently facilitates HLA-I/peptide complex translocation into the endoplasmic reticulum. After glycosylation within the Golgi apparatus, these complexes are migrated to the cell membrane, enabling CTL to recognize displayed peptides. CTL epitopes are typically short peptides of 8-11 residues. The class II (HLA-II) region includes three classical genes coding for HLA-I α and beta (β) chain (DR, DP, and DQ). These molecules acquire peptides from exogenous pathways and present them on the surface of myeloid dendritic cells (DCs), the principal innate professional antigen-presenting cells, thereby allowing naïve $CD4^+$ T lymphocytes to recognize these peptides. This interaction drives their activation into several subpopulations of T helper (Th) lymphocytes, including follicular Th lymphocytes, Th1 lymphocytes, Th2 lymphocytes, Th17 lymphocytes, and regulatory T lymphocytes (Tregs). $CD4^+$ T-cell epitopes are typically long peptides of 13-20 residues.The class III region encodes proteins implicated in immune regulation and complement pathways.

Because these genes are complex and extremely polymorphic with over 35,000 alleles documented until now [18], they appear to be the most important factor in the susceptibility to AI disorders [19-21] and other side effects [14] after COVID-19 vaccination. Vaccines, including those for influenza, Bacille Calmette-Guérin, and hepatitis B (HBV) can also trigger AI conditions through interactions with HLA molecules [11, 22-24]. HLA-I and II genes, along with non-HLA immunogenetic determinants, contribute to the modulation of both CTL and antibody (Ab) responses triggered by vaccines against influenza, HBV, and SARS-CoV-2 [25-28]. Another important feature of the HLA system is the transmission on haplotypes. Different loci of the HLA-I and II regions, though located in distinct genomic regions, are inherited together more often than random chance would suggest, except for the HLA-DP loci. Significant linkage disequilibrium (LD) was observed across all HLA loci, with notable linkage in conserved haplotypes, particularly between the B and C loci in HLA-I, and the DRB1 and DQB1 loci in HLA-II, likely due to their close genomic proximity. Research has revealed correlations between DR-DQ haplotypes and immune responses after the second dose of various vaccines. In particular, HLA-II haplotypes are crucial for presenting vaccine epitopes and influencing immune responses, including cytokine production, across diverse racial and ethnic groups [29, 30].

HLA-peptide binding groove contains multiple distinct pockets or cavities (generally six or more) that are preferentially located in the β-pleated sheet forming the floor of the groove, interacting with specific amino acid (aa) side chains from peptides. Because these pockets are lined by aa residues, which differ from one HLA molecule to another, they appear to be the most important factor in the specificity of peptide binding.

HLA variation and COVID-19 vaccine response

All currently licensed COVID-19 vaccines are designed to target the spike (S) glycoprotein, a critical component that facilitates the transfer of the SARS-CoV-2 viral genome inside alveolar epithelial cells. These vaccines induce protective immunity, mainly via neutralizing antibodies (nAbs) that play an important role in reducing SARS-CoV-2 infection severity and mortality [31]. However, some subjects, particularly uninfected individuals with comorbidities, fail to

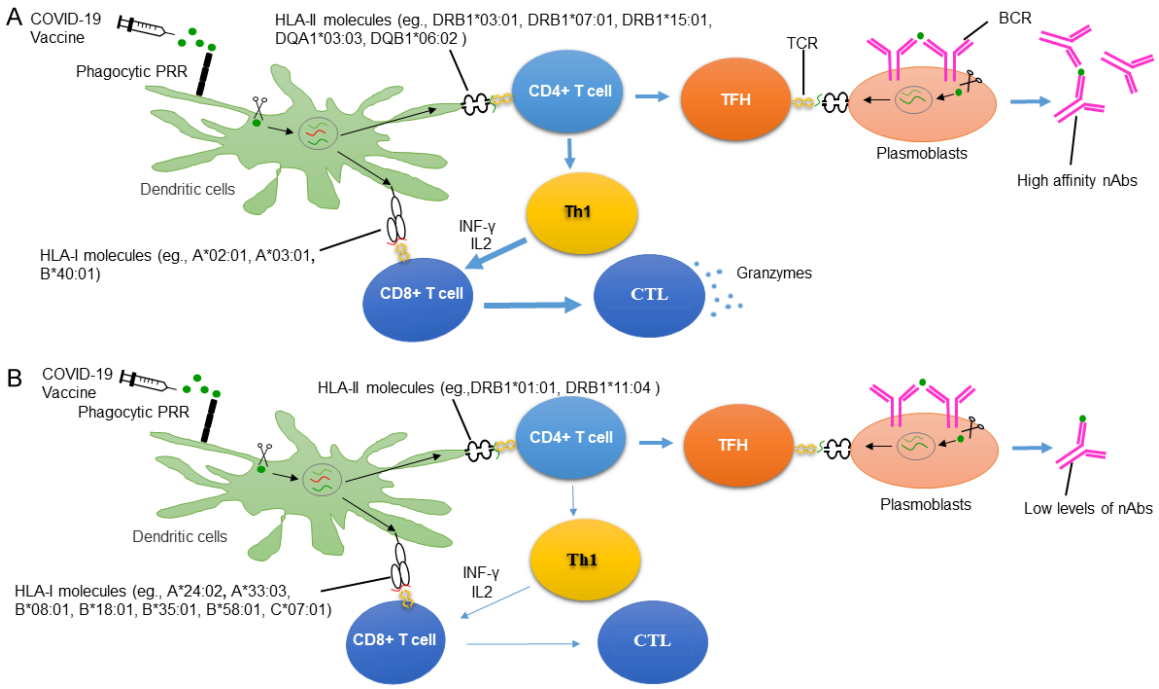

Figure 1. The Role of HLA alleles in immune responses to COVID-19 vaccination. A. Higher nAb levels are associated with the HLA alleles A*02:01 and B*40:01, while DRB1*15:01 and DQB1*06:02 are associated with higher IFN-γ production, indicating a stronger Th1-mediated immune response. B. Lower nAb levels are linked to alleles such as A*33:03 and B*08:01. Specific HLA haplotypes, including A*24:02-B*18:01-C*07:01-DRB1*11:04, are associated with lower antibody titers. COVID-19: Coronavirus Disease 2019; HLA: Human Leukocyte Antigen; CTL: Cytotoxic T Lymphocyte; nAb: Neutralizing Antibodies; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; IFN-γ: Interferon-Gamma; Th1: T helper 1.

achieve sustained protective titers of nAbs after SARS-CoV-2 vaccination, necessitating booster doses [32]. Moreover, 5-10% of immunologically competent subjects do not achieve protective levels of anti-HB surface Abs (≥ 10 mIU/mL) following standard HBV immunization regimens [33]. Genetic differences in HLA genes and haplotypes significantly contribute to interindividual variability in immune responses elicited by vaccines [12, 34-37]. This section summarizes the immunogenetic correlations between HLA alleles and haplotypes and the variability in immune reactions to COVID-19 vaccines in apparently healthy people and patients with AI diseases.

HLA alleles and COVID-19 vaccine response in apparently healthy people

An expanding body of research is currently exploring the influence of HLA-I and HLA-II alleles on Ab and T cell responses to COVID-19 vaccinations in apparently healthy individuals across diverse populations. Specifically, certain HLA-I alleles, including A*33:03, B*08:01, B*18:01, B*35:01, B*58:01, and C*07:01, as well as the HLA-II allele DRB1*01:01, have been associated with lower levels of nAbs against S protein [25, 38-40]. Conversely, other HLA-I alleles, such as A*02:01, A*03:01, and B*40:01, along with HLA-II alleles DRB1*03:01, DRB1*07:01, DQB1*06:02, and DQA1*03:03, have been correlated with higher nAbs levels following the administration of two doses of vaccination [12, 25, 37, 40-42] (**Figure 1**). Additionally, after a single vaccine dose, the DRB1*04:04 allele has been correlated with reduced levels of S-specific IgG Abs, particularly in subjects with a documented past exposure to infection with SARS-CoV-2 virus [41]. This finding underscores the complexity of immune response, suggesting that previous SARS-CoV-2 infection may influence genetic impact on vaccine efficacy. Nevertheless, such associations have not been replicated in other studies, suggesting that IgG anti-S Ab levels are influenced by individual characteristics unrelated to the HLA context [43, 44].

Several studies have also linked HLA variations to differences in Ab response against other vaccines. For example, within the classical HLA-I genes, the HLA-B*45:01 allele is associated with enhanced anti-rubella Ab production following two vaccine doses, whereas the HLA-B*27:05 allele has been linked to lower IgG titers [35]. Among HLA-II alleles, DPA1*02:01 exhibits a relationship with reduced IgG responses against rubella, whereas DPB1*04:01 is linked to elevated Ab levels after two doses [35]. In addition, HLA-B*7 and HLA-B*51 alleles have been identified as contributors to seropositivity after a single dose of measles vaccination, while the HLA-B*8, HLA-B*13, and HLA-B*44 alleles have been implicated in IgG seronegativity following a single dose of the measles vaccine [45].

A significant correlation between HLA genes and SARS-CoV-2-specific interferon-gamma (IFN-γ) production, a marker of Th1-mediated immunity, among healthy subjects following COVID-19 vaccination has been explored. Notably, the allelic frequencies of DRB1*15:01 and DQB1*06:02 have significantly correlated with IFN-γ release following COVID-19 vaccination [41, 46]. In the same way, the HLA-A loci have been correlated to IFN-γ secretion following other vaccines. Ovsyannikova et al. showed that HLA-A*02:01, A*24:02, and A*68:01 alleles are strongly associated with IFN-γ production in white healthy subjects following the rubella vaccine [47]. In agreement, another study suggests that higher levels of IFN-γ were associated with the HLA-A*31:01 allele in schoolchildren after the second administration of the mumps, measles, and rubella (MMR) vaccine [48]. Thus, the genetic variation in HLA alleles may account for individual differences in the IFN-γ response to COVID-19 vaccination.

Genetic variations of HLA-I and HLA-II alleles may also have an impact on COVID-19 outcomes. HLA-DQB1*06 allele is linked to decreased susceptibility to breakthrough infections following vaccination [12]. Indeed, HLA-B*35:01 and HLA-DRB1*01:01 alleles are correlated with reduced duration of COVID-19 [39].

HLA haplotypes and COVID-19 vaccine response in apparently healthy people

Associations between Ab responses and HLA haplotypes have been reported following COVID-19 vaccination in healthy subjects. For instance, the high haplotype frequency of A*24:02-B*18:01-C*07:01-DRB1*11:04 has been shown to correlate with reduced anti-S Ab levels post-vaccination [38]. Moreover, the DRB1*13:02-DQB1*06:04-DQA1*01:02 haplotype is strongly implicated in protecting against seronegativity following the first dose of the vaccine. However, among seropositive individuals, this haplotype has also been linked to an elevated risk of symptomatic COVID-19, suggesting that the DRB1*13:02 allele may contribute to severe disease outcomes [13]. This variability in Ab responses, influenced by HLA haplotypes, is also observed in response to other viral vaccines. Notably, Nishida et al. showed that the HLA-DRB1*04:05-DQB1*04:01 haplotype is linked to decreased Ab responses to the HVB vaccines [49]. However, no significant correlation was observed between HLA haplotypes and Ab responses to the mumps vaccine [50].

Polymorphism of antigen processing and COVID-19 vaccine response

Synthesis of HLA-I and HLA-II molecules into functional complex with antigenic peptides requires the coordination of multiple steps, including antigen processing, peptide transport, loading into the HLA peptide-binding groove, and subsequent expression of HLA/peptide complex on the cell surface. COVID-19 vaccine-induced immune responses could be influenced by polymorphisms and expression levels of genes implicated in antigen processing and presentation pathways. First, the estimated expression levels of the TAP2 and the proteasome subunit beta type-9 (PSMB9) in $CD16^{+}$ neutrophils have been strongly linked to a lack of Ab response following COVID-19 vaccination [13]. Similarly, homozygosity for the TAP allele has been significantly linked to seronegativity after the measles vaccine [51]. These results suggest that variations in antigen processing gene expression may contribute to impaired Ab responses triggered by COVID-19 vaccines. Furthermore, the high variability in aa residues within the pockets of the HLA peptide-binding groove can partly account for inter-individual variations in COVID-19 vaccine-induced immune responses. A recent study involving 100,298 individuals in the United Kingdom found two genetic correlations: the

DRB1*13:02 allele and a substitution of arginine by glycine at aa position 71 in the HLA-DRβ1 pocket 4, with Ab levels after either the first or second dose of SARS-CoV-2 vaccination [13].

HLA alleles and COVID-19 vaccine response in patients with AI diseases

Individuals with AI disorders face increased susceptibility to COVID-19 and reduced vaccine efficacy due to disease-induced immunosuppression and immunomodulatory treatments, with genetic factors like HLA alleles potentially playing a role in modulating immune responses to vaccination. In Japanese individuals with rheumatoid arthritis (RA), HLA-DRB1*15:01 and HLA-DQB1*06:02 alleles have been related to higher concentrations of nAbs against SARS-CoV-2 post-vaccination, suggesting that some genetic backgrounds may enhance vaccine-induced immunity [42]. However, no similar association was found between DRB1*15 and the development of multiple sclerosis following COVID-19 vaccination [52].

Non-HLA genetic polymorphisms and COVID-19 vaccine response

The association between cytokine genes and IgG Ab responses to the S protein in healthy individuals following COVID-19 vaccination has been studied. Scola et al. [53] found that polymorphisms in specific cytokine genes influence Ab response levels to the BNT162b2 vaccine. In particular, 105 days after receiving the recombinant RNA vaccination, a significant correlation was observed between elevated anti-S Ab concentrations and the interleukin-1 receptor 1 (IL-1R1) gene rs2234650. Additionally, individuals with higher post-vaccination SARS-CoV-2 Ab levels more frequently exhibit the IL4 rs2243250 CT genotype. There is also evidence suggesting a link between vaccine-induced immunity and polymorphisms in cytokines and HLA genes. For example, genetic factors such as the DRB1*07 allele, single nucleotide polymorphisms (SNPs) within the IL-2 and IL-4 cytokine genes, and the IL-12B gene indel mutations have been independently linked to HBV vaccine unresponsiveness [26]. Additionally, two variants in the gene of IL-2, rs2069762, and rs2069763, have been linked to increased Ab production and enhanced T cell reactions after vaccination against measles [54]. Conversely, rs1800871, rs1800872, and rs1800890 in the IL-10 gene are linked to decreased Ab responses following measles vaccination.

AI disorders attributed to COVID-19 vaccines

Several AI conditions have been observed in apparently healthy recipients following COVID-19 vaccination, with females being twice as likely as males to develop these disorders. These AI phenomena can generally be subdivided into two groups: organ-specific and systemic AI disorders.

Organ-specific conditions observed in recipients of the COVID-19 vaccine include mainly AI hepatitis (AIH) [55, 56], T1DM [57-59], AI hemolytic anemia (AIHA) [60-62], atypical hemolytic uremic syndrome [63], IgA nephropathy [64-67], and bullous pemphigoid (BP) [3]. The relationship between COVID-19 vaccination and the clinical manifestations of these disorders is more conflicting. There is some evidence that the onset of BP in vaccinated females has been associated with COVID-19 vaccination, suggesting that gender may influence disease susceptibility [3]. This finding is further supported by Tomayko et al., who reported that women aged 40 years and older may be at higher risk of vaccine-associated BP [68]. Contrary to this, some studies have failed to replicate these findings and refuted any association between several AI disorders such as acute AIH and T1DM, and mRNA COVID-19 vaccines [69, 70]. Consistent with these findings, a Swedish case-control study found no significant link between T1DM and several vaccines, including those for tetanus, smallpox, rubella, mumps, and pertussis [71].

Systemic AI disorders following COVID-19 vaccines may be transient, such as immune thrombocytopenic purpura [72, 73] and vaccine-induced thrombotic thrombocytopenia (VITT) [74-76]), or they can lead to chronic disabilities, including systemic lupus erythematosus (SLE) [77-79], RA [80-82], antiphospholipid syndrome (APS) [83, 84], anti-neutrophil cytoplasmic AutoAbs (ANCA)-related systemic vasculitis (AAV) [85-87], and giant cell arteritis (GCA) [88, 89]. A case-control study utilizing data from the Korea Disease Control and Prevention Agency investigated the effects of mRNA SARS-CoV-2 vaccines on connective AI diseases [3].

Analyzing 4,629,401 vaccinated individuals and 4,629,402 controls revealed no significant increased risk of most connective AI disorders following mRNA vaccination. However, a 1.16-fold elevated risk of developing SLE was observed in association with COVID-19 vaccination [3]. While most COVID-19 vaccines appear safe for individuals with pre-existing SLE, reports indicate occasional disease flare-ups following immunization [90]. Additionally, reduced IgG Ab production and IFNγ levels have been documented in these patients, likely attributable to the frequent administration of immunosuppressive and immunomodulatory therapies and the underlying condition [91, 92].

COVID-19 vaccines have also been shown to primarily alter the function of the nervous system and the neuromuscular junction, with reported conditions including Guillain-Barré syndrome [93-95], myasthenia gravis [96], multiple sclerosis [97-99], optic neuritis [100], acute disseminated encephalomyelitis [101], acute transverse myelitis [102], and aseptic meningitis [103].

AutoAbs induced by COVID-19 vaccines

AI conditions can be identified and monitored effectively by analyzing AutoAbs in conjunction with clinical symptoms. Like other viral infections, SARS-CoV-2 has been widely identified as a potential inducer of the de novo development of AutoAbs [104], including nuclear AutoAbs (ANA) [105], antiphospholipid Abs [106], and type I interferon (IFN-I) Abs [106]. COVID-19 vaccination has also been implicated in autoAb production, both in healthy subjects and those with pre-existing AI diseases.

Pathogenic IgG AutoAbs targeting the complex of platelet-bound factor 4 (PF4) chemokine/polyanion were generated in subjects vaccinated with Johnson & Johnson or AstraZeneca COVID-19 vaccines [107-109]. It is suggested that PF4/polyanion complex can act as an autoantigen, potentially stimulating autoreactive T cells or impairing the negative selection of Tregs [5]. In addition, low levels of non-pathogenic IgG AutoAbs have been observed in healthcare workers [74], implying that some individuals may already have an altered immune tolerance due to prior sensitization. The induction of these AutoAbs following COVID-19 vaccination was analysed in 831 Dutch healthcare workers who received mRNA and recombinant adenovirus SARS-CoV-2 vaccines [110]. The levels of PF4 AutoAbs remained consistent among individuals who received either recombinant or mRNA COVID-19, suggesting that both vaccine types have a non-significant impact on PF4 antibodies levels in healthy populations.

Induction of ANA AutoAbs prior to vaccine administration at 3 and 12 months post-SARS-CoV-2 immunisation was assessed in 155 medical staff and clinicians immunized with mRNA vaccines [111]. ANA, AutoAbs against smooth muscle, citrullinated protein antibodies, ANCA antibodies, and anti-phospholipid antibodies were tested. During the study period, 28.57% of individuals developed de nove ANA following COVID-19 vaccination. Among these, ANA positivity appeared to increase with the administration of additional SARS-CoV-2 vaccine doses: 7.79% were positive after two doses, while 16 subjects (20.78%) were positive after three doses.

Previous studies have documented transient emergence of AutoAbs in clinically healthy individuals following several vaccinations. Martinuc et al. screened for several AutoAbs, including ANA, anticardiolipin/anti-β2-glycoprotein I (aCL/β2-GPI), and anti-extractable nuclear antigens Abs pre- and post-vaccination in 85 individuals who received three doses of HVB vaccine [112]. While no systemic rise in autoAb levels occurred, transient low-to-moderate aCL/β2-GPI positivity emerged in three participants at 1 month, resolving by 6 months; one individual showed progressive anti-β2-GPI elevation without clinical symptoms. Another study in 92 healthcare workers receiving non-adjuvanted influenza vaccines revealed that 15% and 13% developed new or elevated AutoAbs at 1 and 6 months post-vaccination, respectively [113]. Persistent elevations (8% of participants) included progressive IgM aCL or IgA β2-GPI in two cases, while 11 exhibited transient Ab spikes. Neither cohort displayed AI disease manifestations during follow-up, underscoring that vaccine-triggered AutoAbs rarely correlate with pathology in non-predisposed populations.

HLA variation and COVID-19 vaccine-induced autoimmunity

SARS-CoV-2 vaccination has been hypothesized to trigger inflammatory and AI responses, particularly in individuals with specific HLA genes and haplotypes. In this section, an overview of the HLA loci associated with AI conditions reported following SARS-CoV-2 vaccines is presented (**Table 1**).

HLA and organ-specific AI disorders following SARS-CoV-2 vaccination

HLA and COVID-19 vaccine-induced AIH

AIH is an AI liver disease primarily mediated by $CD4^+$ T helper (Th) subsets [114], affecting approximately 1 in every 100,000 individuals annually worldwide [115]. About 35 patients with AIH have been documented worldwide in several ethnic groups after receiving various types of vaccines against SARS-CoV-2 [116]. The involvement of Th subsets in AIH pathogenesis is consistent with the strong genetic associations observed at HLA class II loci, particularly HLA-DRB1 [117-120]. Specifically, DRB1*04:04/05 alleles have been positively associated with AIH in populations from Mexico, Japan, and Argentina, while DRB1*03:01/04:01 alleles are linked to AIH type 1 in North American and European groups [121, 122]. Recently, Izagirre et al. [123] reported that Spanish patients who developed AIH following SARS-CoV-2 vaccination carried DRB1*03:01 and DRB1*04 alleles, suggesting that vaccine-triggered AIH may arise in individuals with the same immunogenetic background that predisposes to idiopathic AIH. Furthermore, DRB1 loci have also been correlated to the prognosis of AIH. Notably, Ueno et al. [124] documented a severe case of AIH triggered by SARS-CoV-2 vaccination, with HLA-DRB1 testing confirming the presence of DRB1*04, a genetic factor predisposing individuals to AIH. However, Ghielmetti et al. [125] failed to replicate these findings and instead reported the presence of DRB1*01:01 and DRB1*11:01 alleles in a critical case of AI-like hepatitis following mRNA SARS-CoV-2 vaccine. Interestingly, DRB1*11:01 may confer a protective effect against primary biliary cholangitis (PBC) [126]. These findings suggest that certain HLA-DR molecules may present hepatic autoantigens or vaccine-derived peptides that mimic liver proteins, thereby promoting $CD4^+$ T cell activation and differentiation into different subsets of Th cells. Th1 cells induce liver damage by activating CTLs, while Th2 cells promote AutoAbs production by autoreactive B cells.

HLA and COVID-19 vaccine-induced myocarditis

COVID-19 vaccine-induced myocarditis (VIM) has now been recognized as an uncommon AI disorder [127, 128], particularly affecting young adult men [128]. Experimental models support the role of HLA in myocarditis susceptibility, as non-obese diabetic transgenic mice expressing HLA-DQ8 spontaneously develop myocarditis [129]. VIM has been associated with HLA-DRB1*14:01 and HLA-DRB1*15:03 alleles in the Israeli population [130]. These patients typically present with a benign and self-resolving form of VIM [131]. These data suggest that HLA alleles may influence both VIM susceptibility and progression. In agreement, another study suggests that HLA alleles may contribute to variability in disease course. In fact, the HLA-DQB1*03:03 allele is overrepresented in subjects with myocarditis without cardiac dysfunction compared to healthy controls [132]. HLA alleles have also been associated with other forms of myocarditis. Notably, the HLA-C*07:01 allele has been linked to increased susceptibility to clozapine-related myocarditis in subjects with schizophrenia [133]. Interestingly, a transient increase in the levels of neutralizing IL-1RA AutoAbs has been observed in these patients, suggesting a potential role in disease onset [134-136]. Thus, these findings suggest that the interaction between HLA class II molecules and IL-1RA AutoAbs may influence VIM susceptibility and onset. However, the precise relationship between HLA alleles and IL-1RA AutoAbs remains unclear.

Beyond HLA genes, variations in HLA-I ligands have been associated with VIM susceptibility. Tsang et al. reported that killer cell immunoglobulin like receptor (KIR)2DS3 + /KIR2DL5B/KIR2DS4del + /KIR2DS5 haplotype correlated with an increased risk of acute VIM among Chinese adolescent [137], implicating natural killer (NK) lymphocytes in its pathogenesis. Disruption of HLA-I molecules and KIR interaction can enhance NK cell-mediated cytotoxicity,

Table 1. Reported cases of COVID-19 vaccine-induced autoimmunity and HLA

Type of vaccine	HLA	Disease	Population	Reference
Viral vector; mRNA	DRB1*03:01, DRB1*04	Vaccine-induced autoimmune hepatitis	Four cases (Spain)	Izagirre et al. [123]
mRNA (three doses)	DRB1*04	Steroid-refractory autoimmune hepatitis after COVID-19 vaccination	One patient (Japan)	Ueno et al. [124]
mRNA	DRB1*01:01, DRB1*11:01	Severe vaccine-induced autoimmune hepatitis	One Caucasian patient	Ghielmetti et al. [125]
mRNA	DRB1*14:01, DRB1*15:03	Vaccine-Induced Myocarditis	29 patients and 300 healthy controls (Israel)	Aharon et al. [130]
ChAdOx1 nCoV-19 vaccine	DRB1*11; DPB1*17:01, DQA1*05:01, DQB1*02:01, and DRB1*11:04	Vaccine-induced thrombotic thrombocytopenia	One patient (Denmark); Sixteen patients (Italy)	Tølbøll Sørensen et al. [144], Petito et al. [141]
mRNA; Inactive vaccine (CoronaVac)	B*35, C*04; A*11-B*35-C*04 haplotype; A*01, A*03:01, A*11	Vaccine-induced subacute thyroiditis	14 patients, 100 healthy controls (Turkey); 27 patients, 362 healthy donors (Turkey); Two cases (Poland)	Şendur et al. [151], Sahin et al. [20], Stasiak et al. [155]
ChAdOx1 nCoV-19; mRNA-1273 (Moderna)	DR4, DRB1*09:01	Vaccine-induced ANCA-related systemic vasculitis	2 cases (Taiwan); 1 case (Japan)	Loo et al. [19], Kawamura et al. [21]
	DRB1*15:02	Vaccine-induced glomerulonephritis	1 case (Japan)	Nagai et al. [182]
m-RNA; viral vector	DRB1*04	Vaccine-induced giant cell arteritis	12 patients (France)	Liozon et al. [187]
m-RNA	DRB1*04:04	Vaccine-induced polymyalgia rheumatica	1 case (Japan)	Yokote et al. [190]
m-RNA; viral vector	DRB1*03:01, DRB1*04, DRB1*11:01	Vaccine-induced antisynthetase syndrome	23 patients (Spain)	García-Bravo et al. [197]
m-RNA	DRB1*04:05:01-DQB1*04:01:01; DRB1*09:01-DQB1*03:03; DRB1*13:02:01-DQB1*06:04:01	Vaccine induced-insulin-dependent diabetes mellitus	1 case (Japan); 1 case (Japan); 1 case (Japan)	Sasaki et al. [59], Yano et al. [57], Sato et al. [168]
m-RNA	DRB1*15:02, DRB1*04:05	Vaccine-induced systemic lupus erythematosus	2 cases (Japan)	Sakai and co-workers [200]
m-RNA	B*51	Behçet's Disease-associated panuveitis after COVID-19 vaccination	1 case (Taiwan)	Lin et al. [204]

potentially contributing to myocardial damage. In parallel, increased levels of $CD57^+$ NK lymphocytes have been observed in male individuals with VIM [137]. Interestingly, increased IL-18 levels were also reported in a male patient with VIM [138]. IL-18 might be responsible for KIR downregulation on NK cells, thereby enhancing NK cell activity without directly altering HLA-I expression levels [139].

HLA and VITT

VITT is an immune-mediated thrombotic disorder, potentially triggered by AutoAbs targeting PF4 and polyanion (P) complex following adenovirus-based COVID-19 vaccination. This disorder predominantly affects young women in their second and fifth decades of life [140]. The mechanisms underlying the production of these AutoAbs remain unclear, likely arising from a complex interplay between environmental and genetic determinants.

Polymorphisms in HLA-II alleles are associated with VITT. An observational case-control study conducted in Italy, involving sixteen subjects with VITT following adenoviral COVID-19 vaccination, demonstrated an elevated allelic frequency of DQA1*05:01, DQB1*02:01, DRB1*11:04, and DPB1*17:01 compared to controls subjects [141]. Notably, PF4-derived peptide containing specific residues (Glu28 and Ala32) demonstrates a strong binding affinity for the HLA-II DRB1*11:04 molecule [141], highlighting its relevance in antigen presentation to Th lymphocytes and thymus-dependent Ab responses. This epitope also corresponds to the residues on PF4 that are recognized by VITT anti-PF4 AutoAbs, further implicating its role in the pathogenesis of VITT [142, 143]. In the same way, Tølbøll Sørensen and workers reported a rare case of severe VITT following adenovirus-based vaccination. HLA-II testing revealed the presence of the DQB1*03/05; DRB1*01/11; and DPB1*02:01/04:01 alleles [144]. HLA-DRB1*11 has been previously associated with other AI disorders that result in thrombosis among Caucasian populations in several European studies. Notably, HLA-DRB1*11 has consistently been linked to a higher risk of acquired thrombocytopenic thrombotic purpura (TTP) [145, 146]. Furthermore, HLA-DRB1*11 is closely associated with DRB3*01:01, which has been recognized as a potential trigger of heparin-induced thrombocytopenia (HIT) [147]. Additionally, another study suggested an association between the rs6903608 variant, located within the HLA-II locus, and the DQB1*05:03 allele in acquired TTP [148].

Despite the fact that the association between HLA-DR-DQ haplotypes and VITT has not reported, it is notable that DRB1*11:04 is an LD with DQA1*05:01 in European population. Indeed, the DRB1*03:01-DQB1*02:01 haplotype has been shown to be associated with the development of PF4/heparin Abs in individuals with HIT [149].

Thus, these findings indicate that VITT may share a similar feature with these coagulopathies AI conditions, potentially involving antigen presentation of PF4-derived peptide by HLA-II molecules.

HLA and COVID-19 vaccine-induced SAT

SAT induced by COVID-19 vaccination represents an AI and inflammatory thyroid disorder that may emerge following immunization.

SAT is linked to certain HLA alleles. In 2021, the relationship between vaccine-induced SAT and HLA-B*35 was initially documented through a study conducted on individuals experienced SAT in Poland [150]. This association has since been confirmed across various ethnic populations, including those in Turkey [20, 151], Japan [152], and Ireland [153]. A case-control study conducted in Turkey, involving 14 subjects with COVID-19 vaccine-induced SAT and 100 healthy controls, revealed that 93% of the patients carried B*35 and C*04 alleles. Moreover, homozygosity for these alleles has been associated with thyrotoxicosis and a severe inflammatory response [151]. LD analysis by Sahin et al. demonstrated that the A*11-B*35-C*04 haplotype is strongly linked to vaccine-induced SAT in the Turkish population [20]. Given the substantial genetic LD between the C*04 and B*35 alleles [154], the C*04 allele alone cannot be regarded as an independent immunogenetic predisposing factor for vaccine-induced SAT. In addition to the established relationship between the B*35 allele and COVID-19 vaccine-induced SAT, several cases have also involved class I HLA-A alleles, including A*01 [151], A*03:01 [155] and A*11 [20].

HLA-B*35 was additionally identified as being linked to SAT following influenza vaccination in subjects from various ethnic populations [8, 9]. The C*04 and B*35 alleles, belong to the HLA-I region, are known for their role in presenting antigens that trigger T-cell-mediated immune reactions against thyroid autoantigens in SAT.

The proposed mechanism explaining the relationship between vaccine-induced SAT and B*35 allele involves exposure to vaccine adjuvants. This hypothesis is supported by the observed association between SAT and several inactivated and subunit vaccines [156-159].

HLA and COVID-19 vaccine-induced T1DM

T1DM induced by COVID-19 vaccination represents an AI disorder that may emerge following immunization [160-163]. It is associated with specific HLA alleles and haplotypes. Notably, HLA-DRB1*04:05:01-DQB1*04:01:01 [59] and HLA-DRB1*09:01-DQB1*03:03 [57, 164] have been associated with the onset of T1DM following COVID-19 vaccination. Both HLA haplotypes are well-established genetic factors involved in T1DM susceptibility in East Asian populations [165-167]. The recurrence of the same HLA haplotypes following other vaccines, such as influenza vaccination [10], strongly suggests that both influenza and SARS-CoV-2 vaccines are not inherently diabetogenic but rather act as non-specific immune triggers in patients with pre-existing HLA genetic susceptibility.

It is noteworthy that the inclusion of HLA-DRB1*13:02:01-DQB1*06:04 as a potential risk haplotype for T1DM onset following COVID-19 vaccination [168] warrants caution. This haplotype is generally considered neutral or only weakly associated with T1DM [169]. Moreover, it is too early to deduce from a single patient that this haplotype significantly affects T1DM susceptibility after COVID-19 vaccination [170]. Further studies with larger cohorts are required to confirm this association.

Thus, SARS-CoV-2 vaccination could trigger T1DM onset in patients carrying a pre-existing HLA genetic predisposition.

HLA and systemic AI diseases following COVID-19 vaccination

Recently, numerous reports and studies have attempted to link the occurrence of non-organ-specific or systemic AI conditions, which can affect multiple organs and systems, and specific HLA alleles or haplotypes in vaccinated individuals. These disorders include systemic vasculitis and connective tissue diseases. Below is a compilation of selected COVID-19 vaccination-induced systemic AI diseases, along with suggested HLA allele associations at both the individual and population levels.

HLA and COVID-19-induced systemic vasculitis

Systemic vasculitis constitutes a spectrum of conditions marked by intense systemic inflammation affecting the vascular system. Following vaccination against SARS-CoV-2, rare but severe systemic vasculitis has been documented. These include ANCA-related systemic vasculitis (AAV) [85, 87, 171], cryoglobulinemic vasculitis [172], IgA vasculitis [173], hypocomplementemic urticarial vasculitis [174], anti-glomerular basement membrane (GBM) disease [175], polyarteritis nodosa [176] and GCA [177-179]. The role of HLA alleles in susceptibility to these conditions has been explored in several studies across diverse ethnic populations.

In AAV, the most notable association was found in the DR locus [19, 21], which aligns with a previously reported correlation between myeloperoxidase-ANCA and DRB1*09:01 in a Japanese population [180] as well as DR4 in a Dutch population [181]. The HLA-DRB1*09:01 variant is commonly found in East Asian cohorts, yet it is infrequent in European populations.

Nagai et al. [182] documented a case of anti-GBM glomerulonephritis after vaccination against SARS-CoV-2 in Japan. HLA class II testing revealed the presence of the DRB1*15:02 allele. Nevertheless, the DRB1*15:01 allele is strongly associated with anti-GBM disorder in various ethnic populations [183-185].

GCA is characterized by chronic granulomatous inflammation, primarily involving Th1 cells. These cells predominantly produce IFN-γ, which is crucial for macrophage stimulation and enhances the expression of HLA-II in synovial fibroblasts [186]. A case-series study involving sixteen subjects with COVID-19 vaccine-induced GCA in France showed that 54% of the individuals were positive for the DRB1*04 allele [187]. This finding aligns with previous

reports identifying HLA-DRB1 04 as a major immunogenetic risk factor for GCA [188]. However, Che et al. [189] failed to replicate this finding and instead reported a correlation between HLA-DRB1*16:02 and an increased susceptibility to bilateral ischemic optic neuropathy from GCA following vaccination against SARS-CoV-2 in South Korea. While this suggests a potential role for DRB1 16:02 in disease susceptibility, conclusions drawn from a single patient must be interpreted cautiously, as further validation is required to establish its relevance to vaccine-induced GCA.

HLA and polymyalgia rheumatica following SARS-CoV-2 vaccination

PMR is a rare inflammatory rheumatic condition primarily affecting elderly patients, causing muscle pain and stiffness, particularly in the hips and shoulders. The coexistence of PMR and GCA may result from gene-environment interactions. Associations between certain HLA-II alleles and PMR have been explored in both isolated cases of the condition and in its co-occurrence with GCA.

Yokote et al. [190] performed HLA analysis in a 71-year-old woman who developed isolated PMR ten days following the first dose of mRNA COVID-19 vaccine. The authors identified the DRB1*04:04 allele, which was also found in the case described by Perez and Maravi after a seasonal influenza vaccine [191]. The allelic frequency of DRB1*04:04 ranges from 0.012 to 0.028 in East Asian individuals [192]. Additionally, Jarrot et al. [193] identified an increased phenotypic frequency of the DRB1*04:01 in 20% of PMR/GCA subjects following SARS-CoV-2 vaccination, highlighting a genetic susceptibility previously observed in GCA [188] and PMR [194]. This allele may play a crucial role in the immuno-pathogenesis of these conditions. Notably, individuals with isolated PMR who carry DRB1*04 alleles, especially DRB1*04:01, have shown a higher frequency of disease relapses [195]. This allele is considered a genetic risk factor for PMR but does not directly cause the disease. Therefore, it is hypothesized that older individuals with a predisposition to the DRB1*04 allele may have an increased susceptibility to the development of vaccine-induced PMR, potentially due to the strong immunological response triggered by the mRNA vaccine against SARS-CoV-2. Moreover, the allelic distribution of DRB1*13:01 has been found to be more common in PMR patients compared to those with GCA [193]. Liozon et al. documented a significant positive association between PMR and DRB1*13:01 allele in older subjects with PMR/CGA-induced by influenza vaccination [11]. Further case studies incorporating both HLA typing and SARS-CoV-2 Ab titers are necessary to explore the association between DRB1 and PMR/GCA after vaccination against SARS-CoV-2. Such research is essential for identifying individuals at higher risk for this rare condition.

HLA and antisynthetase syndrome following COVID-19 vaccination

Antisynthetase syndrome (ASS) is a rare inflammatory myopathy associated with anti-RNA-synthetase AutoAbs, with Jo-1 being the most well-known. The condition is characterized by a range of symptoms, including interstitial lung disease, inflammatory arthritis without joint deformities, fever, mechanic's hands, Raynaud's phenomenon, and myositis.

Recent case studies have documented the emergence of ASS related to immunisation against COVID-19 [187, 196, 197]. The role of pathogenic high-affinity AutoAbs against RNA-synthetases in COVID-19 vaccine-induced ASS suggests an interaction between B and Th lymphocytes. Moreover, Th lymphocyte stimulation requires T-cell receptor engagement with the HLA-RNA synthetase peptide complex, indicating that HLA-II molecules may be genetic predisposition factors for ASS. This hypothesis has shown promise, with investigations identifying DRB1*11:01, DRB1*04, and DRB1*03:01 alleles as genetic susceptibility factors in individuals with COVID-19 vaccine-induced ASS [197]. Similarly, Sugimoto et al. documented a rare case of dermatomyositis with melanoma differentiation-associated gene 5 (MDA5) Abs following COVID-19 vaccination, where HLA-II testing revealed the presence of the DRB1*04:05 variant [198].

The DRB1*03:01-B1*08:01 haplotype was also found in a patient with dermatomyositis who experienced clinical worsening following COVID-19 vaccination [197]. Similar findings were observed in several other investigations. In a comprehensive case-control analysis, the

B1*08:01-DRB1*03:01 haplotype has been identified as a significant immuno-genetic risk factor for ASS in Spanish individuals of European ancestry [199]. This finding is further supported by the observation that HLA-DRB1*03:01 allele is significantly correlated with positivity for anti-Jo-1 Abs, with a frequency of 31.80% in individuals positive for anti-Jo-1 Abs compared to 15.50% in those negative for anti-Jo-1 Abs.

HLA and SLE following COVID-19 vaccination

Vaccine-induced SLE is a rare side effect occurring after several vaccines, including SARS-CoV-2 and HBV vaccines. The onset of this complication involves both genetic and environmental factors. In fact, Sakai *et al.* [200] reported two cases of SLE induced by mRNA-based COVID-19 vaccine in Japan. Laboratory findings revealed specific HLA-I alleles, including HLA-A (*11:01, *24:02, *24:20) and HLA-B (*52:01, *55:02, B*46:01), and HLA-II alleles HLA-DRB1 (*04:05, *15:02), HLA-DPB1 (*04:01, *05:01, *09:01), and HLA-DQB1 (*04:01, *06:01). The HLA-DRB1*15:02 allele is a well-established genetic factor involved in SLE susceptibility among Southeast Asian populations [201], reinforcing its potential role in vaccine-induced SLE. This case adds to the growing evidence linking vaccine-induced SLE to specific HLA alleles. Similarly, Santoro *et al.* [202] reported a rare case of HBV vaccine-induced lupus nephritis, where HLA typing revealed the presence of HLA-A*24:03/25:05, -B*18:25, -DRB1*11:02/11:32, -DQA1*05:05, and -DQB1*03:01. Further investigation through large cohort studies is needed to establish a link between vaccine-induced SLE and specific HLA alleles [203].

HLA and COVID-19 vaccine-induced Behçet's disease

Behçet's disorder (BD), an autoinflammatory syndrome, is marked by recurring ulcerations in the oral cavity and genital regions, skin lesions, and inflammatory eye disorders, with a notable association with genetic factors, especially the HLA-B*51 allele.

Recently, Lin et al. [204] reported a rare case of BD-associated panuveitis in a young Taiwanese male after receiving the initial dose of mRNA COVID-19 vaccine. HLA-I testing confirmed the presence of the B*51 allele, a well-established risk factor for both BD and its ocular complications, including posterior uveitis and visual impairment [205]. This finding aligns with previous evidence linking HLA-B*51 to the pathogenesis of BD and its severe ocular manifestations. On the other hand, Tagini et al. [206] were unable to replicate this finding and documented a case of mRNA vaccine-induced BD in a young Caucasian female who lacked the HLA-B*51 allele. Interestingly, the absence of this allele corresponds with the mucocutaneous form of BD, which is more commonly seen in younger women [207]. Further insights into the role of specific HLA alleles in BD pathogenesis have emerged from studies conducted in Thailand. These investigations underscore the significance of the HLA-B*51:01 allele subtype as a critical immunogenetic marker linked to posterior uveitis and visual impairment [208]. Additionally, the HLA-A*26:01 has been identified as a contributing risk factor in individuals who are negative for B*51, highlighting the complexity of genetic contributions to BD susceptibility [208]. The allelic distribution of B*51 varies significantly across different ethnic groups and populations. For instance, it is strongly associated with populations across regions historically linked by the ancient Silk Road, including Turkey, North Africa, and East Asia, where BD is more prevalent [209].

Thus, it is too early to establish conclusive evidence regarding the implication of B*51 allele and B5 antigen in the development of vaccine-induced BD.

Mechanisms of COVID-19 vaccine-induced AI disorders

COVID-19 vaccine-induced AI disorders result from a complex interplay of pathways and events that allow autoreactivity to manifest and cause self-sustaining tissue damage. Mechanisms include HLA gene predisposition, modification of autoantigen structure (e.g., via post-translational modifications and exposure of cryptic epitopes), antigen mimicry, and acquisition of adjuvant properties by disease-specific autoantigens.

HLA gene predisposition

Vaccines are identified by the immune components as external antigens and interact with T-cell or B-cell receptors, thereby initiating an

Table 2. Possible mechanisms for involvement of HLA in COVID-19 vaccine-induced autoimmunity

Mechanism	Description	Example (s)
Alteration of self peptide structure	Certain HLA-II molecules may present cryptic antigens, either activating self-reactive Th lymphocytes or failing to properly engage Treg lymphocytes.	Anti-PF4/P antibodies in VITT
Postranslational modifications of self antigens	HLA alleles have a high affinity for modified peptides, especially if the modification alters the peptide's fit in the HLA binding groove. The presentation of these modified peptides differs from the normal presentation of unmodified self-peptides.	Hyperphosphorylated IL-1RA in Vaccine Induced Myocarditis
Molecular mimicry	HLA molecules present peptides that mimic self-antigens, leading to immune responses against self-tissues.	Molecular mimicry between spike epitopes of mRNA vaccines and self-epitopes

adaptive immune response. Nevertheless, the mechanism linking HLA genes to autoimmunity triggered by COVID-19 vaccines remains incompletely understood, with several hypotheses proposed to clarify this relationship (**Table 2**).

First, polymorphisms in HLA alleles may influence the clinical progression of vaccine-induced AI. As discussed above, homozygosity for HLA-C*04 and -B*35 alleles could be associated with poorer outcomes in vaccine-induced SAT [151].

Second, variations in the peptide-binding grooves of HLA molecules may modulate COVID-19 vaccine-induced autoimmunity. The HLA peptide-binding groove comprises several distinct pockets that form the floor of the groove and interact with specific aa side chains from peptides. Variations in the aa composition of the HLA-A binding cavity B and the HLA-DR binding cavities P4, P7, and P9 could affect antigen presentation in VIM [130].

Third, LD between a disease-associated HLA allele and a nearby genomic element within the same haplotype that actually causes the disease, rather than the HLA molecule itself, may account for these associations. For instance, in T1DM, the observed association with HLA-DQ/DR alleles is attributed to mutations in the insulin gene promoter, which is in LD with HLA-II loci [210]. Similarly, SLE shows a strong association with complement C4 gene deletions, which impair immune complex clearance. These deletions are situated within the HLA-III region and are in LD with HLA-DR3/DR2 haplotypes [211, 212].

While immune reactivity to self-antigens in COVID-19 vaccine-induced autoimmunity is often attributed to HLA-restricted antigen presentation, it is worth noting that the actual responsible antigen may originate from a different locus within the haplotype or be linked through LD.

Modification of autoantigen structure

Several potential mechanisms may alter antigen processing and expose cryptic epitopes. The vaccine or its components (e.g., polyanion (P)) may covalently bind to an endogenous peptide (e.g., PF4) to form a cryptic antigen complex [5, 213]. In this model, the cryptic antigen complex acts as an altered self-peptide, potentially activating self-reactive T helper lymphocytes or failing to properly engage regulatory T lymphocytes due to the abnormal presentation of epitopes by HLA-II molecules. This process results in the development of Ab responses specifically targeting the vaccine (e.g., anti-PF4/P antibodies in VITT). Another potential mechanism involves IL-1RA hyperphosphorylation, which has been related to VIM [134]. Protein phosphorylation is crucial for the physiological function of numerous proteins, and an increased risk of VIM has been established in 75% of subjects with neutralizing antibodies against IL-1RA [134], especially those carrying the HLA-II DRB1*14:01/15:03 alleles [130].

Antigen mimicry

Antigen mimicry has frequently been proposed as a potential initiator of AI diseases. AI responses associated with COVID-19 vaccines may result from cross-reactivity or molecular mimicry between spike epitopes of the mRNA vaccines and self-epitopes in certain ethnic populations [104]. This phenomenon is also

involved in hepatitis B vaccine induced-multiple sclerosis [214].

Adjuvants

Adjuvants can trigger AI symptoms in genetically susceptible individuals. Work by Shoenfeld and colleagues provided important initial support for this concept [215]. They described the autoimmune/inflammatory syndrome induced by adjuvants (ASIA), which may occur following exposure to immune-stimulatory adjuvants. Several case reports and small case series have documented ASIA-like presentations after COVID-19 vaccination, including polymyalgia rheumatica and SAT [216, 217]. However, further studies are required to confirm the role of adjuvants in the development of COVID-19 vaccine-induced AI disorders.

Clinical implications and future research

A clinical assessment, including a detailed vaccination history and evaluation of comorbidities, is essential for all individuals meeting the diagnostic criteria for AI diseases. Given the consequent underestimation of post-COVID-19 vaccine-induced AI disorders, heightened vigilance and systematic documentation are warranted in clinical practice. In addition, a thorough risk-benefit evaluation should be conducted before administering further vaccinations or boosters to subjects with pre-existing AI diseases who are in clinical remission.

Two primary approaches are used to study the relationship between HLA genes and AI diseases. The first involves population studies, comparing the distribution, frequency, and variation of HLA loci within and across different human populations with those of healthy controls. Notably, three case-control studies have demonstrated significant associations between HLA-I [151] and HLA-II alleles [130, 141] and AI conditions induced by COVID-19 vaccines. The second approach focuses on family studies, investigating whether affected relatives exhibit a higher frequency of shared HLA haplotypes than would be expected based on general genetic inheritance patterns. However, to date, no family studies have been conducted to investigate associations between HLA haplotypes or HLA homozygosity and COVID-19 vaccine-induced AI. This highlights a gap in current knowledge and underscores the need for future investigations into familial clustering and HLA-related genetic susceptibility in this context.

Several technologies are available for HLA typing, each with distinct advantages and limitations. Commonly used methods include oligonucleotide-based hybridization arrays (SSO), polymerase chain reaction (PCR)-driven primer systems (SSP), dideoxy chain-termination sequencing (SBT), and next-generation sequencing (NGS). However, the presence of an HLA allele or haplotype does not always correspond to its functional expression at the cell surface. Thus, future studies should clarify the relationship between HLA expression and AI diseases induced by SARS-CoV-2 vaccines.

More questions than answers

Susceptibility conferred by HLA in COVID-19 vaccine-induced autoimmunity exhibits ethnic specificity. Several key questions, however, remain unanswered. Firstly, the precise mechanisms underlying susceptibility to such autoimmunity remain elusive, necessitating further investigation into the specific interactions between HLA molecules and autoantigens implicated in vaccine-induced AI. Additionally, the high polymorphism of HLA genes poses significant challenges in determining how particular alleles influence disease susceptibility, severity, and progression. Although HLA molecules are crucial for T cell activation, the specific peptides presented in AI contexts have not been fully characterized. Moreover, while HLA alleles predispose individuals to AI diseases, environmental parameters also contribute to disease development.

While a significant number of these correlations are found within HLA-I and II loci, large-scale genomic analyses employing SNP markers have revealed that, beyond these HLA loci, the entire HLA region contains numerous SNPs associated with various disorders or traits. Notably, as much as 90% of genetic variants linked to AI conditions have been mapped to noncoding regions of the genome [218]. As a result, it is plausible that disease-related elements may be distributed not just within HLA loci, but also throughout the broader HLA region. A key regulatory element within the noncoding regions of the HLA is microRNA (miRNA), which plays an important role in gene expression modulation. An analysis of functional ele-

ments within these regions identified 113 microRNAs (miRNAs), including mmu-miR-721 (has-miR-Chr8:96), which is transcribed from an intronic region of the HLA-DRB1 gene. Consequently, has-miR-Chr8:96, a microRNA specific to myocarditis, has shown potential as a marker for acute myocarditis [219]. Thus, a comprehensive understanding of disease pathogenesis requires thorough exploration of the interplay between HLA genetics, noncoding RNAs (miRNAs or long noncoding RNAs) and environmental triggers, including infections, diet, and lifestyle factors. Further research in these areas is essential for advancing our understanding of COVID-19 vaccine-induced autoimmunity and informing strategies for its prevention and management.

Disclosure of conflict of interest

None.

Abbreviations

COVID-19, Coronavirus Disease 2019; HLA, Human Leukocyte Antigen; CTL, Cytotoxic T Lymphocytes; Nabs, Neutralizing Antibodies; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; IFN-γ, Interferon-Gamma; Th1, T helper 1; PSMB9, Proteasome Subunit Beta Type-9; TAP2, Transporter Associated with Antigen Processing 2; AIH, Autoimmune Hepatitis; T1DM, Type 1 Diabetes Mellitus; AIHA, Autoimmune Hemolytic Anemia; VITT, Vaccine-Induced Thrombotic Thrombocytopenia; APS, Antiphospholipid Syndrome; ANCA, Anti-Neutrophil Cytoplasmic Antibodies; AAV, ANCA-Related Systemic Vasculitis; GCA, Giant Cell Arteritis; ANA, Antinuclear Antibodies; VIM, Vaccine-Induced Myocarditis; IL-1RA, Interleukin-1 Receptor Antagonist; SAT, Subacute Thyroiditis; TTP, Thrombotic Thrombocytopenic Purpura; HIT, Heparin-Induced Thrombocytopenia; PBC, Primary Biliary Cholangitis; PMR, Polymyalgia Rheumatica; ASS, Antisynthetase Syndrome; Jo-1, Histidyl-tRNA Synthetase Autoantibody; PCR, Polymerase Chain Reaction; SSP, Sequence-Specific Primer; SSO, Sequence-Specific Oligonucleotide; SBT, Sanger Sequencing-Based Typing; NGS, Next-Generation Sequencing.

Address correspondence to: Abdellatif Bouayad, Department of Immunology, Faculty of Medicine and Pharmacy, 4867 University of Oujda, Oujda 60049, Morocco. E-mail: a.bouayad@ump.ac.ma

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