Research suggests HLA & HNA may play a critical role in COVID-19 Susceptibility, Immune Protection and Success of Novel Treatments during a Global Pandemic Crisis

Abstract:
Of vital contemporary importance, the human immune response to many viral pathogens is heavily contingent on the background human leukocyte antigen (HLA) repertoire of the infected individual. As the current COVID-19 pandemic evolves, research is indicating that HLA type may play an integral role in population level immune monitoring and vaccine development. Additionally, the emerging importance of convalescent plasma therapy as a treatment for COVID-19 infection propagates the need for full HLA and human neutrophil antigen (HNA) donor antibody screening to mitigate the risks of TRALI development.

Key Considerations:
• Any impact that HLA genetics have on the response to SARS-COV-2 is not yet clear. Further HLA association studies are urgently required and may vary by geographical location.
• For convalescent plasma therapy trials to be effective, the significant risk of TRALI induction should be mitigated.

Background:
HLA Association with COVID-19 Disease Severity

Variation in the immune response to viral antigen is a complex process governed and controlled by variation in the genes that encodes the components of our immune system. HLA genes, in particular, have been shown to be instrumental in affecting both susceptibility and the response to viral infection. Previous studies that investigated the immune response to West Nile Virus (WNV), for example, showed that some virus derived proteins are preferentially presented to the immune system in the context of a limited repertoire of HLA antigens—in this instance HLA-A*02:01.

During the current pandemic, the disease called COVID-19 is caused by the virus severe acute respiratory syndrome 2 (SARS-COV-2). Great efforts are currently underway to assess how variability across the classical HLA genes may affect both susceptibility to and severity of the disease. Following the first SARS outbreak which originated in Shunde, located in Gungdong Province of China in November 2002, large numbers of HLA association studies were then published over the following years. Conclusive findings from these studies were often hindered by confirmation bias, small sample sizes, and shortcomings associated with the insufficient resolution offered by some of the HLA typing methodologies used. HLA-B*07:03, B*46:01, DRB1*03:01 are all examples of HLA alleles reported to have increased susceptibility to the original SARS disease whilst other studies suggested that no HLA association could be found and therefore that HLA was unlikely to play a role in disease susceptibility or severity of progression.

Fast forward to 2020 and already there are a growing number of reports emerging on the possible association of certain HLA alleles with SARS-COV-2 susceptibility and more severe disease progression. Once more, the HLA allele B*46:01 has been suggested to have the capability to process and present the fewest number of potential viral peptides, thus leaving individuals at increased susceptibility of the most severe disease progression. Conversely, patients who carry the HLA-B*15-03 allele may present the widest repertoire of viral peptides, rendering these individuals, at least in theory, some degree of immune protection.

As a result, HLA typing will provide valuable information to assist researchers in exploring transmission prevention, treatment modalities, and vaccination approaches. As it has long been established that HLA polymorphism exhibits high degrees of regional characterization, it is important to consider that HLA alleles which confer either increased susceptibility or prevention will likely vary with geography. The increased susceptibility of the HLA-B*46:01 allele in SARS related pathologies is also likely influenced by the increased prevalence of the HLA-B*46:01 allele in individuals of Asian origin; in a North American or European sample cohort, it is highly unlikely that HLA-B*46:01 will be associated with increased disease susceptibility due to the extremely low frequency of the allele in the populations. Thus, when one considers the high infection rates across outbreak epicenters from Europe to the US, it is highly likely that there are other HLA alleles conferring differential viral responses in these areas.
The key work to identify the relevant alleles is ongoing and requires the HLA typing of large numbers of individuals in order to confidently define these alleles at the population level. In keeping with other models of HLA restricted disease pathogenicity, susceptibility alleles may be numerous but could share a number of structural similarities that limit the repertoire of potential viral peptides able to be presented to the circulating T-cells. By the same token, the alleles shown to confer a degree of immunological protection may display sequence homology that lends itself to the potential presentation of a wider range of viral target peptides.

Identifying by virtue of HLA status those at risk of developing severe SARS-COV-2 is key to many elements in the overall pandemic response. However, for those in whom infection has already occurred and symptoms have reached serious levels, there is an urgent need to identify and trial novel therapeutic interventions. One such innovative approach that has launched numerous international feasibility trials is the use of convalescent plasma therapies to mitigate disease symptoms and reduce the incidence of ventilator support in COVID patients and to subsequently reduce the required period of hospitalization.

**HLA and HNA Role in COVID-19 Treatment**

As the name suggests, convalescent plasma therapy involves the infusion of plasma taken from patients who have recovered from COVID-19 infection. These plasma donors will be assumed to have immunity from the infection and as such will be able to transfer their acquired humoral immunity to the virus to the patient. The passage of these COVID-specific antibodies has the potential to reduce the severity of the infection and to accelerate the recovery period. However, even in emergency situations such as those currently experienced during the pandemic, there is always a requirement to adhere to all relevant safety protocols and to follow the transfusion best practice guidelines for the medical center trialing the therapy. Of particularly acute need in COVID-19 cases is the close adherence to the transfusion guidelines for mitigating the risk of Transfusion related acute lung injury (TRALI). TRALI is a potentially life-threatening pulmonary transfusion reaction characterized by lung edema, occurring within six hours post-transfusion.

TRALI is thought to be a two-step process. Under normal conditions, the lung vasculature still contains substantial numbers of neutrophils. These neutrophils can become partially activated by pulmonary tissue inflammation (usually of unknown origin but in COVID patients, may occur as a consequence of the hallmark associated cytokine storm), but may still remain below the threshold for TRALI development. A second trigger is required for TRALI to develop; this is trigger is the transfer of antibodies from various forms of transfusion products to the patient. Fresh frozen plasma (FFP), platelets, and packed red blood cells have all been implicated with TRALI due to high plasma volume. In the COVID setting, this second trigger may occur due to the administration of the convalescent plasma donation. Neutrophil activation leads to the disruption of the pulmonary endothelial barrier and a subsequent edema, possibly due to the release of reactive oxygen species by activated neutrophils.

To ensure a COVID patient receiving convalescent serum does not develop TRALI, the donated blood should be screened for both HLA-I and HLA-II antibodies, as well as Human Neutrophil Antigen (HNA) antibodies per recommended guidelines.

- Class I HLA-specific antibodies can bind directly to lung endothelium or to donor white blood cells, leading to neutrophil activation.
- Class II HLA-specific antibodies are thought to bind to MHC class II expressed on recipient monocytes, which in turn can activate neutrophils.
- Human neutrophil antigen (HNA) specific antibodies are also important and can directly bind and activate recipient neutrophils. HNA-3a antibodies are most common and have been implicated in numerous reported TRALI fatalities.

Relevant national transfusion guidelines will vary by region. For example, in the U.S. HLA antibody screening is mandatory, but in the UK and many other parts of Europe, guidelines also clearly call for the HNA antibody status to be determined as well prior to plasma infusion.
Solutions:

HLA Susceptibility Studies:
- LABType products are reverse SSO DNA typing assays that provide superior resolution for HLA A, B, C, DRB1, DRB3, DRB4, DRB5, DQA1, DQB1, DPA1, and DPB1 HLA typing. The multiplex analysis dramatically reduces labor, reagents, reaction-to-reaction inconsistencies, and assay time associated with a multi-well format assay making it a cost-effective solution. No more handling of strips or membranes, colorimetric reactions, nor visual analysis of colored bands or dots.
- The newly added LABType XR and CWD assays, exclusively designed for use with the LABScan3D™, allow multiplexing of up to 500 bead regions allowing for a broader combination of detection probes for a single sample.
- AllType offers a complete NGS solution that delivers unambiguous, high-resolution genotyping results in less than three days. This assay delivers single tube amplification for all eleven Class I and Class II loci, completely removing the need for amplicon pooling. Samples are transferred directly to library preparation and made ready for sequencing in a single workday.
- The AllType FASTplex™ NGS assay combines the convenience of multiplex PCR with workflow simplicity by eliminating most of the pipetting, purification, and quantification steps required by traditional methods. By pooling amplicons into a single tube in the first hour, libraries can be prepared for sequencing with minimal hands-on time.

Convalescent plasma therapy support:

To mitigate the risk of TRALI and to ensure the timely identification of eligible donors, it is imperative to be able to assess rapidly and accurately each potential donor for the presence of HLA and/or HNA antibody negativity. The One Lambda brand, produced by the Transplant Diagnostics Division of Thermo Fisher Scientific, is the clear leader in this area, offering a range of antibody detection solutions to cover all specificity, sensitivity, budgetary and throughput requirements. the LABScreen product family offers a range of powerful tools, including the only FDA-cleared and CE-marked IVD test available on the market which enables the simultaneous detection of both anti-HLA and anti-HNA antibodies. All of the LABScreen tests provide a familiar easy workflow that allows for efficient batch testing of up to 96 samples per run.
- LABScreen Multi (LSMUTR) – The only FDA-cleared IVD test for simultaneous detection of HLA Class I, HLA Class II, and HNA antibodies (including HNA-1a, 1b, 2, and 3a).
- LABScreen Mixed (LSM12) – Simple, low resolution screening test for detecting the presence of HLA Class I and Class II antibodies.
- LABScreen PRA (LS12PRA) – Intermediate resolution and sensitivity screening test for detecting HLA Class I and Class II antibodies.
- LABScreen Single Antigen Classic (LS1A04, LS2A01) – Highest resolution and sensitivity LABScreen test for identifying HLA Class I and Class II antibody specificities.
- LABScreen Single Antigen ExPlex (LS1AEX01, LS2AEX01) – Expanded panel that can be used in combination with Single Antigen Classic to identify a broader range of HLA antibody specificities.

Please note that for the research applications related to COVID-19, the products listed in this white paper are for Research Use Only and Not for Use in Diagnostic Procedures.

Conclusion: Polymorphism in the host HLA is likely to play a key role in the pathogenicity of COVID-19. Understanding the precise nature of this influence is key to successful treatment and vaccine development. One Lambda is perfectly positioned to drive these investigations from research into the clinic via our comprehensive portfolio of HLA typing solutions. Additionally, One Lambda has the requisite HLA and HNA antibody screening products to protect patients from adverse transfusion related lung injury during upcoming convalescent plasma therapy trials.
References


