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Current HLA Investigations on SARS-CoV-2 and Perspectives

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The rapid, global spread of the SARS-CoV-2 virus during the current pandemic has triggered numerous efforts in clinical and research settings to better understand the host genetics' interactions and the severity of COVID-19. Due to the established major role played by MHC/HLA polymorphism in infectious disease course and susceptibility, immunologists and geneticists have teamed up to investigate its contribution to the SARS-CoV-2 infection and COVID-19 progression. A major goal of the Covid-19|HLA & Immunogenetics Consortium is to support and unify these efforts. Here, we present a review of HLA immunogenomics studies in the SARS-CoV-2 pandemic and reflect on the role of various HLA data, their limitation and future perspectives.

Keywords: MHC, HLA, association analysis, SARS-CoV-2, COVID-19, immunogenetics

THE ROLE OF IMMUNOGENETICS IN INFECTIOUS DISEASES

The SARS-CoV-2 Pandemic

In late 2019, hospitals in Wuhan, China, received patients with pneumonia symptoms of unknown origin (Zhu et al., 2020). Researchers quickly identified the cause of this disease, a novel member of the coronavirus family, a single-strand RNA virus further named SARS-CoV-2 by the WHO on February 11th, 2020. This infection led to COVID-19 disease. It can progress towards the development of an acute respiratory distress syndrome (ARDS) which can be lethal, especially but not exclusively, in older patients and patients with comorbidities (Ruan et al., 2020; Zhou et al., 2020). Previous coronavirus outbreaks, in 2003 with SARS-CoV and 2012 with MERS, had already demonstrated the danger of these known zoonotic viruses for humans (Shi and Hu, 2008). Contrary to SARS-CoV and MERS, which were successfully contained, but caused almost a thousand deaths each, SARS-CoV-2 is still active and endangering human health. In the span of almost 2 years, the virus spread to at least 240 million individuals, leading to more than 4.8 million deaths across the globe (O (2021).oronavir, 2021). The greater scale of this pandemic may be explained by the higher rates of transmission observed, the common asymptomatic carriers and the various severity of infected people (Syangtan et al., 2021).

Researchers determined that SARS-CoV-2 shares 50–79.5% of global sequence similarity with MERS and SARS-CoV, respectively, and that the mechanism of SARS-CoV-2 infection is similar to SARS-CoV, such as highlighted by Guo et al. (Guo et al., 2020). Their viral spike protein, found on the envelope, binds to the ACE2 receptor to enter human cells. While the virus spread globally and

on a large scale, multiple SARS-CoV-2 strains have now emerged as the virus mutates, particularly presenting variations in the spike protein, such as the Gamma variant (P.1) in Brazil and the Delta variant (B.1.617.2) in India. These new strains provide a great incentive to assess the possible effects on immunity of such modifications (Burki, 2021), mainly because vaccines were designed to target the original spike protein.

Understanding the host response and the effect of host genomics is key for understanding variation in disease course subsequent to SARS-CoV-2 infection. Initial reports about COVID-19 suggested a pathogenic role of the immune system in the disease, damaging the lungs in a cytokine-storm provoked by CD4⁺ T lymphocytes and monocytes (Zhou et al., 2020). This excessive reaction in the wake of SARS-CoV-2 infection seems to be confirmed in non-human primates with less severe illness in animals with anti-inflammatory responses (Fahlberg et al., 2020). The COVID Human Genetic Effort has investigated these cellular responses at the genetic and genomic levels, describing rare variants in the *IFN* and *TLR* genes in patients with severe symptoms (Zhang et al., 2020a; Bastard et al., 2020; Zhang et al., 2020b; Casanova et al., 2020). Additionally, association studies have identified polymorphisms in the chemokine receptors and *IFN*, validating their role (Pairo-Castineira et al., 2020; The Severe Covid-19, 2020; D-19 Host Genetics In, 2021). On the genomic level, multiple studies have identified potentially important genes for COVID-19 severity and susceptibility, and researchers organized in different consortia, such as the COVID-19 Host Genetics Initiative, have collected association studies for meta-analyses (Pairo-Castineira et al., 2020; The Severe Covid-19, 2020; Mayoral et al., 2020; Ganna et al., 2020; Castro de Moura et al., 2021). In the same collective spirit, the COVID-19|HLA & Immunogenetics Consortium was created to investigate the role of the most polymorphic region of the human genome, the Major Histocompatibility Complex (MHC), in particular the Human Leukocyte Antigen (HLA) genes which are known to be highly associated with infectious diseases (Chen et al., 2011; Garcia et al., 2013; Spínola, 2016; Sawai et al., 2018; Thoens et al., 2018; Sanchez-Mazas, 2020a). In this review, we acknowledge recent advances linking HLA variation with COVID-19 and advocate for further progress in these efforts.

Linking HLA and Infectious Diseases: From SNP to HLA Allele

In the past decade, genome-wide association studies (GWAS) have become an essential tool for exploring the link between genetic background and complex phenotypes (Visscher et al., 2017). Rather than focusing efforts on candidate genes, DNA genotyping chips recover Single Nucleotide Polymorphisms (SNP) genotypes along the entire genome. Significant genotype-phenotype associations can be identified by comparing the SNP frequency in one population with a continuous trait (e.g., height, viral load) or between two populations differing by a binary trait or disease (e.g., HIV-1 infected patients vs general population). Contrary to Mendelian genetics, GWAS results are characterized by common genetic variants (allelic frequency ≥ 0.5 –1%) associated with a low to

moderate effect size on the outcome of interest, illustrating the “common variant-common disease” hypothesis. Identification of individual SNP contributions allows an overall burden evaluation of the disease genetic risk (Khera et al., 2018) (or protection) and a better understanding of molecular pathophysiological pathways. The GWAS catalog (EMBL-EBI, 2021) was created in 2008 to compile all GWAS results (Welter et al., 2014; MacArthur et al., 2017) and now contain 300,000 associations from 5,000 independent studies (October 6th, 2021).

Numerous SNPs in the vicinity of *HLA* genes were confirmed to be associated with diseases (Price et al., 1999), and, the extended MHC accounts for 2.5% of all significant associations (Figure 1), and a third of significant chromosome 6 associations.

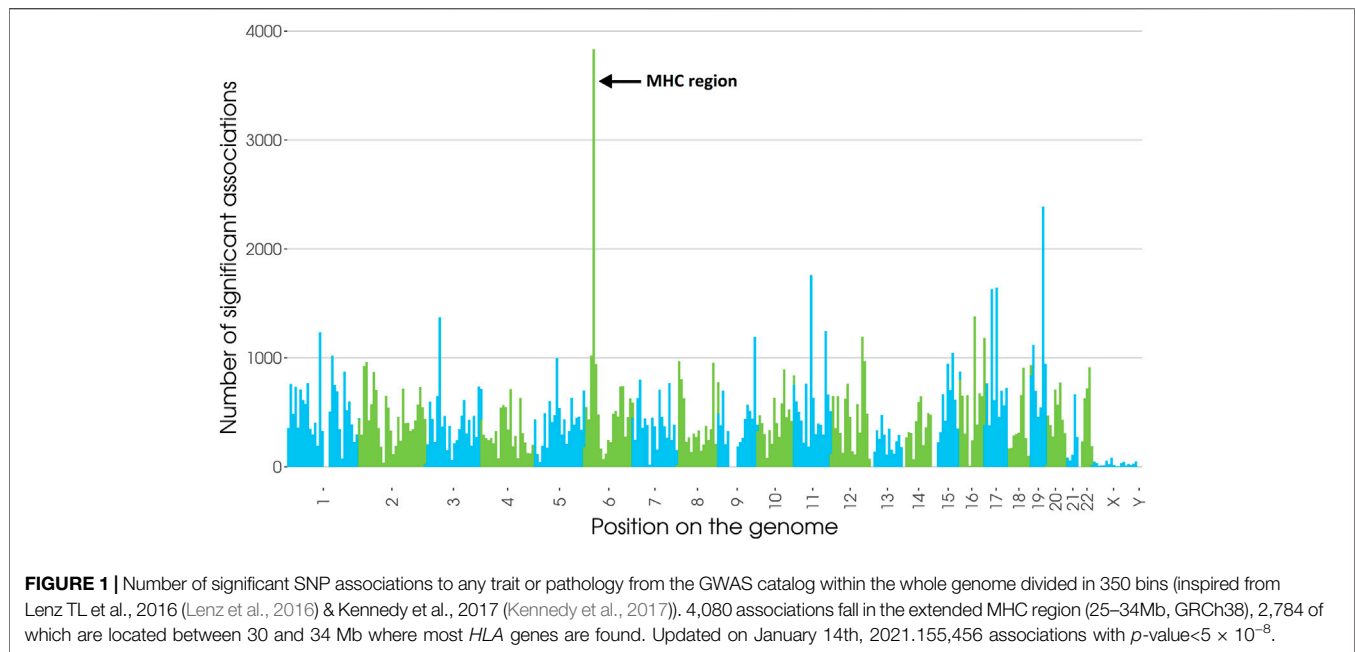
Additionally, 21% of all traits in the catalog have at least one association in the extended *MHC*, illustrating the crucial role of *MHC* polymorphisms in human health. As expected, associations near the *MHC* region are immunity-related, from infectious diseases (Sanchez-Mazas, 2020a), to auto-immunity (Dendrou et al., 2018).

For example, one of the most significant *HLA* associations with an infectious disease is for *HLA-B*57* tagging SNPs (SNPs not in an *HLA* gene but in linkage disequilibrium, LD, with specific *HLA* alleles) with HIV (OR = 3.47) (Fellay et al., 2007; Limou et al., 2008; Le Clerc et al., 2009; Limou et al., 2009). The rs2395029 SNP, which is almost in complete LD with the *HLA-B*57:01* allele, was associated with HIV viral control in Europeans (Limou and Zagury, 2013), and symmetrically, the rs2523608 SNP, likely tagging the *HLA-B*57:03* allele was discovered in African-American patients (Pelak et al., 2010). Other viral diseases showed associations with *HLA* SNPs include Hepatitis B virus (Hu et al., 2013; Jiang et al., 2015), Hepatitis C virus (Lee et al., 2018; Vergara et al., 2019), Epstein-Barr virus (Rubicz et al., 2013), and SARS-CoV (Sanchez-Mazas, 2020b). For a review, please see the extensive report by Sanchez and others (Sanchez-Mazas, 2020a).

However, the fact that GWAS identify a large genetic region associated with an outcome, without directly pinpointing functional, causal variants represents an important challenge for interpreting GWAS results. Such interpretation is made even more difficult by the complex LD patterns of the extended *MHC* region. Additional *HLA* typing and statistical inference of *HLA* alleles can refine the SNP association signals to specific *HLA* alleles, reflecting specific molecular functions and pathways. Such a strategy was successfully implemented for infectious diseases such as HIV, HPV, Dengue, and Ebola (Lin et al., 2003; Wang et al., 2011; Nishida et al., 2016; Adebamowo and Adeyemo, 2019; Chen et al., 2019; Ekenberg et al., 2019; Butler-Laporte et al., 2020; Chaisri et al., 2020; Huang et al., 2020; Ursu et al., 2020; Yengo et al., 2020).

Scope of the Review

Despite the central roles played by the *MHC* region and *HLA* molecules for the study of immune-related disease, understanding the underlying mechanisms of susceptibility and protection is far from complete (Trowsdale and Knight, 2013). The current pandemic raises questions regarding the role of *HLA* in recognition of or immune responses to a new virus. In



this report, we review the first HLA-related investigations of SARS-CoV-2 and advocate for further efforts in HLA and COVID-19 analyses, using modern algorithms and resources, in order to enhance present and future research.

COVID-19 AND HLA ASSOCIATION STUDIES

HLA polymorphisms have previously been closely associated with viral infections and disease outcomes, whether they are associated with protection or susceptibility. The intrinsic diversity of *HLA* molecules and the many possibilities to investigate their link to diseases sparked researchers' interests during this novel pandemic. Researchers have investigated the interaction of host *HLA* diversity on both the infection by SARS-CoV-2 and the severity of the resulting COVID-19.

In Silico Peptide Binding and *HLA* Allele Frequencies

Studies using *in silico* peptide binding and *HLA* allele frequencies rely on available databases which do not require to generate data; thus, they are the first actionable steps to *HLA* analysis. Nguyen et al. proposed the first *in silico* *HLA* approaches in early 2020 by using the reference amino acid sequence of the SARS-CoV-2 (with NCBI accession number, NCBI:txid2697049) along with the netMHCpan software to predict the class I *HLA* alleles most susceptible to presenting SARS-CoV-2 peptides (Nguyen et al., 2020). They identified *HLA-B*46:01* as the least presenting allele and *HLA-B*15:03* as the most presenting one, possible risk and protective factors of infection, respectively. This publication was highlighted in the immunogenetics section of *Nature*, creating a starting point for *HLA* researchers (Zahn, 2020). Later, La Porta

and others used Artificial Neural Networks to predict the binding capacity of each *HLA* class I allele, also demonstrating *B*46:01* and others as a weak binder, and *B*15:03* as a strong binder (La Porta and Zapperi, 2020). However, their results do not entirely overlap, demonstrating that functional studies should be performed. Barquera and others performed a similar analysis also considering *HLA-DRB1* and *HLA-DQA1/DQB1*, indicating many *HLA* alleles (some highly frequent) among the best presenters, including *B*15:03*, and another list of worse presenters, including *B*46:01* (Barquera et al., 2020).

Interestingly, *B*15:03* frequency varies across the globe, with high frequencies in African populations and admixed ones (such as Brazilians), but low frequencies in Asia and Europe. Conversely, *B*46:01* is highly frequent in Asia and rare in the rest of the world. The same dynamics can be observed for most of the alleles in the strong or weak presenter list.

Romero-López et al. expanded this investigation to class II *HLA* alleles and identified multiple *HLA-DP* and *HLA-DR* *HLA* alleles as well as *HLA-A*02:03* as the allele with the most binding affinity to a viral peptide (Romero-López et al., 2020). Further research by de Sousa et al. of the most frequent *HLA* alleles of people from Europe, Asia and Africa and their interaction with variants and seems to point towards a selective pressure of class II MHC only regarding the binding of the ORF8 protein in SARS-CoV-2 (de Sousa et al., 2020).

The first studies only displayed correlations between COVID-19 phenotypes (e.g., incidence, severity, mortality) and *HLA* allele frequencies obtained in the allelefrequencies.net database or from local bone marrow donor registries, notably in Italy, an important European cluster. Correale et al. investigated class I correlations at one-field resolution (Correale et al., 2020). Pisanti et al. took a closer look at *HLA* haplotypes with an Italian registry, and identified *HLA-A*01:01 g ~ B*08:01g ~ C*07:01g ~ DRB1*03:01g* as positively correlated with incidence and *HLA-A*02:01g ~*

*B*18:01g ~ C*07:01g ~ DRB1*11:04g* as negatively correlated with incidence (Pisanti et al., 2020). Some studies took a more global approach by comparing the COVID-19 statistics of every country to their known *HLA* allele frequencies, providing discordant and mostly non-significant results (Ishii, 2020; Sakuraba et al., 2020; Tomita et al., 2020; Toyoshima et al., 2020). Other studies focused on a cellular level and identified a preponderance of monocytes with low expression of *HLA-DR* in infection and severity of SARS-CoV-2 (Benlyamani et al., 2020; Zmijewski and Pittet, 2020; Kreutmair et al., 2021; Roussel et al., 2021).

HLA Association Studies

Later, *HLA* association studies of various sample sizes tried to evaluate the direct link between *HLA* and different COVID-19 phenotypes. Wang et al. inferred the *HLA* class I and class II genotypes of 332 Chinese individuals to compare severe and mild cases of COVID-19, using xHLA (Xie et al., 2017) and SOAP-*HLA* (Cao et al., 2013), two software which allow *HLA* genotyping from sequencing data. *HLA-A*11:01* (p -value = 0.009, OR 2.3), *HLA-B*51:01* (p -value = 0.007, OR 3.3), and *HLA-C*14:02* (p -value = 0.003, OR 4.7) were identified as top signals in the *HLA* class I region (Wang et al., 2020a). Direct *HLA* typing cohorts were also investigated across the world, but with small sample sizes going as high as 190 individuals. No associations were found by Iturrieta-Zuazo et al. in 45 Spanish patients between COVID-19 severity and *HLA* supertypes (Iturrieta-Zuazo et al., 2020), and none was found between mortality at 30 days and *HLA* one-field genotypes from 72 individuals from Canary Islands by Lorente et al. (2021). Three different groups conducted association analyses against a healthy control group to identify susceptibility of infection to SARS-CoV-2: Wang et al. (2020b) compared 82 COVID-19 vs 3,548 controls from China and found *HLA-B*15:27* as associated (p -value = 0.001, OR 3.6), Novelli et al. (2020) compared 99 COVID-19 vs 1,017 controls from Italy and found 3 significant association (*HLA-B*27:07*, p -value = 0.00001; *HLA-DRB1*15:01*, p -value = 0.002; *HLA-DQB1*06:02*, p -value = 0.0001), and Yung et al. (2020) compared 190 COVID-19 vs 3892 controls from Hong-Kong but did not identify any significant association. More recently, Khor et al. (2021) also identified *HLA-A*11:01:01:01* as a risk factor for COVID-19 severity (p -value = 0.003, OR 3.4), in a study involving 190 patients and 423 controls, after controlling for comorbidities and other confounding factors. Shachar et al. (2021) showed no association between COVID-19 severity and *HLA* alleles in a large-scale study of *HLA* typed Israelis ($n = 20,937$), though it was limited to two-field information. Finally, Castro de Moura et al. investigated the relationship between the epigenome of patients and COVID-19 severity from 407 patients and showed differentially methylated probes in *HLA-C* associated with the response of interferon in the viral response (Castro de Moura et al., 2021).

In addition to these studies, the Severe COVID-19 Consortium conducted a genome-wide association study of 1,980 patients of European ancestry and notably investigated *HLA* with classical SNP association, and *HLA* association by NGS genotyping in a subset of individuals. This was the first high-scale

genomics initiative. However, chromosome 3 (*SLC6A20*, *LZTFL1*, *CCR9*, *FYC O 1*, *CXCR6*, and *XCR1*) as well as in the ABO locus (with A as risk and O protective) were the only significantly associated loci (The Severe Covid-19, 2020). The absence of *HLA* association was also shown by the meta-analysis on COVID-19 severity performed by the COVID-19 Human Genetic Initiative (HGI), where a variant in *HLA-G* was found but not replicated (Pairo-Castineira et al., 2020). However, the HGI release 6 in June 2021 identified 5 variants reaching statistical significance within the *CCHCR1* gene, situated 110 kb downstream of *HLA-C* (top SNP: rs111837807, p -value = 2.2×10^{-11} , OR_{meta} 1.23) as well as a variant within *HLA-DPBI* 3'UTR (rs9501257, p -value = 4.1×10^{-8} , OR_{meta} 1.19), when comparing the general population to patients with critical COVID-19 ($n_{cases} = 8,779$, $n_{control} = 1,001,875$, from 25 studies of various ancestries). It is notable that multiple variants linked to *HLA* genes seemed consistent, but not significant, between studies (D-19 Host Genetics In, 2021), which suggests that increasing cohort sizes in the future or running in-depth *HLA*-centric explorations may reveal additional significant signals.

CONCLUSION

Classical large GWAS meta-analysis recently reported SNP associations in the *MHC* region, mostly with critical COVID-19 illness, however the impact of *HLA* molecules might not be as imagined for this novel infectious disease. Unlike HIV-1 infection where *HLA* is the driving signal of viral control and disease progression, impact of *HLA* in SARS-CoV-2 infection seems milder and mostly restricted to severity symptoms, and its role has yet to be fully understood.

Multiple *HLA*-focused analyses performed during the last 2 years have had greatly varying results with inconsistent associations even in large studies [$n = 20,937$ in (Shachar et al., 2021)]. Further direct *HLA* allele association studies could provide the necessary power to carefully assess the role of *HLA* in immune response against SARS-CoV-2, but unfortunately, typing has not been conducted on large samples to date, leading to underpowered studies (most studies with less than 190 individuals). Indeed, *HLA* exploration requires large sample size; the *HLA* system has an important diversity, with thousands of alleles on multiple different genes. In a given population, a few numbers of these alleles are usually sufficient to represent the majority of individuals. However, to understand the role of the *HLA* system in diseases, it is important to also study alleles with a smaller frequency, which may be absent of cohorts with limited sample size.

HLA allele inference from sequencing (WGS and WES) and SNP genotyping data already generated for genome-wide analyses with the support of large biobanks and international consortia should therefore be given a high priority in the near future to provide a definitive answer on the impact of *HLA* molecules on COVID-19 phenotypes. Indeed, promising results from large association meta-analyses showed associations of both class I and class II *HLA* SNPs with severity, in the latest data

release of the COVID-19 Host Genetic Initiative. Furthermore, the study of *HLA* 5-gene haplotype organization, and other immunogenetic parameters such as cell surface expression levels and interaction with KIR ligands may paint a bigger picture on the underlying immunogenetic mechanisms involved in the infection course.

HLA studies reported in this review rely on correlations and moderate size cohorts as stated. However, the COVID-19 crisis created an international collaboration to share data in order to explore host genetics risk factors for different COVID-19 outcomes (D-19 Host Genetics In, 2021). A vast amount of NGS and GWAS data have been generated: 49,562 COVID-19 positive cases vs >2M population controls with GWAS data in the COVID-19 Host Genetics Initiative (D-19 Host Genetics In, 2021); 20,952 cases vs 565,205 controls with WES data in the Regeneron study (Kosmicki et al., 2021). Thinking beyond COVID-19, the large national and international human genomics efforts represent a unique opportunity to promote large-scale HLA-centric analyses and to better describe *HLA* allele diversity across the globe by leveraging novel inference algorithms. These algorithms allow HLA typing from NGS and GWAS data (i.e., xHLA (Xie et al., 2017) and HIBAG (Zheng et al., 2014), respectively). Concerning other immunogenetics parameters, such as 5-gene HLA haplotypes or KIR ligands, it is now possible to infer them with HLA data (Geffard et al., 2020), with a detailed review of these tools in Douillard et al. (2021). Using these tools at a large scale on existing cohorts with GWAS and NGS data will clarify the role of HLA in COVID-19 outcomes and help understanding the mechanisms of the pathology.

The SARS-CoV-2 pandemic has had a huge global health toll, and has sparked a collective effort in the scientific community to identify candidate targets accounting for the diversity in response to the infection. HLA was quickly investigated for links with the

SARS-CoV-2 infection and the resulting COVID-19 disease. The first studies, often underpowered, showed discordant results, and more robust association studies recently suggested a much milder effect of *HLA* SNPs and alleles on COVID-19 phenotypes as foreseen. The choice of the phenotype of interest was also proven to be crucial in association studies, as COVID-19 severity seems to be more closely linked to *HLA*. In this report, the COVID-19|HLA & Immunogenetics Consortium aimed to provide a critical view of current *HLA* analyses and their intrinsic power and limitations. We also hope this report will incite geneticists to run HLA-centric studies by expanding the pool of data available for *HLA* genotyping and genotypes imputation, in order to untangle the precise role of the Major Histocompatibility Complex in COVID-19 outcomes and other immune-related diseases.

AUTHOR CONTRIBUTIONS

VD contributed in writing the review and produced figures. EC, SM, JH, P-A G, NV and SL contributed in writing and editing various sections of the review.

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REFERENCES

- Adebamowo, S. N., and Adeyemo, A. A. (2019). Classical HLA Alleles Are Associated with Prevalent and Persistent Cervical High-Risk HPV Infection in African Women. *Hum. Immunol.* 80 (9), 723–730. doi:10.1016/j.humimm.2019.04.011
- Barquera, R., Collen, E., Di, D., Buhler, S., Teixeira, J., Llamas, B., et al. (2020). Binding Affinities of 438 HLA Proteins to Complete Proteomes of Seven Pandemic Viruses and Distributions of Strongest and Weakest HLA Peptide Binders in Populations Worldwide. *HLA* 96 (3), 277–298. doi:10.1111/tan.13956
- Bastard, P., Rosen, L. B., Zhang, Q., Michailidis, E., Hoffmann, H.-H., Zhang, Y., et al. (2020). Autoantibodies against Type I IFNs in Patients with Life-Threatening COVID-19. *Science* 370 (6515), eabd4585. doi:10.1126/science.abd4585
- Benlyamani, I., Venet, F., Coudereau, R., Gossez, M., and Monneret, G. (2020). Monocyte HLA-DR Measurement by Flow Cytometry in COVID-19 Patients: An Interim Review. *Cytom A* 97 (12), 1217–1221. doi:10.1002/cyto.a.24249
- Burki, T. (20211027). Understanding Variants of SARS-CoV-2. *Lancet* 397, 462. doi:10.1016/s0140-6736(21)00298-1
- Butler-Laporte, G., Kreuzer, D., Nakanishi, T., Harroud, A., Forgetta, V., and Richards, J. B. (2020). Genetic Determinants of Antibody-Mediated Immune Responses to Infectious Diseases Agents: A Genome-wide and HLA Association Study. *Open Forum Infect. Dis.* 7 (11), 1–14. doi:10.1093/ofid/ofaa450
- Cao, H., Wu, J., Wang, Y., Jiang, H., Zhang, T., Liu, X., et al. (2013). An Integrated Tool to Study MHC Region: Accurate SNV Detection and HLA Genes Typing in Human MHC Region Using Targeted High-Throughput Sequencing. *PLoS One* 8 (7), e69388. doi:10.1371/journal.pone.0069388
- Casanova, J.-L., Su, H. C., Abel, L., Aiuti, A., Almuhsen, S., Arias, A. A., et al. (2020). A Global Effort to Define the Human Genetics of Protective Immunity to SARS-CoV-2 Infection. *Cell* 181 (6), 1194–1199. doi:10.1016/j.cell.2020.05.016
- Castro de Moura, M., Davalos, V., Planas-Serra, L., Alvarez-Errico, D., Arribas, C., Ruiz, M., et al. (2021). Epigenome-wide Association Study of COVID-19 Severity with Respiratory Failure. *EBioMedicine* 66, 103339. doi:10.1016/j.ebiom.2021.103339
- Chaisri, S., Jumnainsong, A., Romphruk, A., and Leelayuwat, C. (2020). The Effect of KIR and HLA Polymorphisms on Dengue Infection and Disease Severity in Northeastern Thais. *Med. Microbiol. Immunol.* 209 (5), 613–620. doi:10.1007/s00430-020-00685-z
- Chen, D., McKay, J. D., Clifford, G., Gaborieau, V., Chabrier, A., Waterboer, T., et al. (2011). Genome-wide Association Study of HPV Seropositivity. *Hum. Mol. Genet. [Internet]* 20 (23), 4714–4723. doi:10.1093/hmg/ddr383
- Chen, Y., Liao, Y., Yuan, K., Wu, A., and Liu, L. (2019). HLA-A, -B, -DRB1 Alleles as Genetic Predictive Factors for Dengue Disease: A Systematic Review and Meta-Analysis. *Viral Immunol.* 32 (3), 121–130. doi:10.1089/vim.2018.0151
- Correale, P., Mutti, L., Pentimalli, F., Baglio, G., Saladino, R. E., Sileri, P., et al. (2020). HLA-B*44 and C*01 Prevalence Correlates with Covid19 Spreading across Italy. *Int. J. Mol. Sci. [Internet]* 21 (15), 5205. doi:10.3390/ijms21155205
- COVID-19 Host Genetics Initiative (2021). Mapping the Human Genetic Architecture of COVID-19. *Nature*. doi:10.1038/s41586-021-03767-x

- de Sousa, E., Ligeiro, D., Lérias, J. R., Zhang, C., Agrati, C., Osman, M., et al. (2020). Mortality in COVID-19 Disease Patients: Correlating the Association of Major Histocompatibility Complex (MHC) with Severe Acute Respiratory Syndrome 2 (SARS-CoV-2) Variants. *Int. J. Infect. Dis.* 98, 454–459. doi:10.1016/j.ijid.2020.07.016
- Dendrou, C. A., Petersen, J., Rossjohn, J., and Fugger, L. (2018). HLA Variation and Disease. *Nat. Rev. Immunol.* 18 (5), 325–339. doi:10.1038/nri.2017.143
- Douillard, V., Castelli, E., Mack, S. J., Hollenbach, J., Gourraud, P.-A., Vince, N., et al. (2021). Approaching Genetics through the MHC Lens: Tools and Methods for HLA Research. *Front. Genet.*
- Ekenberg, C., Tang, M.-H., Zucco, A. G., Murray, D. D., MacPherson, C. R., Hu, X., et al. (2019). Association between Single-Nucleotide Polymorphisms in HLA Alleles and Human Immunodeficiency Virus Type 1 Viral Load in Demographically Diverse, Antiretroviral Therapy-Naïve Participants from the Strategic Timing of Antiretroviral Treatment Trial. *J. Infect. Dis.* 220 (8), 1325–1334. doi:10.1093/infdis/jiz294
- Embl-Ebi, N. I. H. (2021). The GWAS Catalog. Available from: <https://www.ebi.ac.uk/gwas>.
- Fahlberg, M., Blair, R., Doyle-Meyers, L., Midkiff, C., Zenere, G., Russell-Lodrigue, K., et al. (2020). Cellular Events of Acute, Resolving or Progressive COVID-19 in SARS-CoV-2 Infected Non-human Primates. *Nat. Commun.* 11 (1), 6078. doi:10.1038/s41467-020-19967-4
- Fellay, J., Shianna, K. V., Ge, D., Colombo, S., Ledergerber, B., Weale, M., et al. (2007). Study of Major Determinants for Host Control of HIV-1. *Science* 317 (August), 944–947. doi:10.1126/science.1143767
- Ganna, A., Unit, T. G., and General, M. (2020). The COVID-19 Host Genetics Initiative, a Global Initiative to Elucidate the Role of Host Genetic Factors in Susceptibility and Severity of the SARS-CoV-2 Virus Pandemic. *Eur. J. Hum. Genet. [Internet]* 28 (6), 715–718. doi:10.1038/s41431-020-0636-6
- Garcia, A., Milet, J., Courtin, D., Sabbagh, A., Massaro, J. D., Castelli, E. C., et al. (2013). Association of HLA-G 3'UTR Polymorphisms with Response to Malaria Infection: A First Insight. *Infect. Genet. Evol.* 16, 263–269. doi:10.1016/j.meegid.2013.02.021
- Geffard, E., Limou, S., Walencik, A., Daya, M., Watson, H., Torgerson, D., et al. (2020). Easy-HLA: a Validated Web Application Suite to Reveal the Full Details of HLA Typing. *Bioinformatics* 36 (7), 2157–2164. doi:10.1093/bioinformatics/btz875
- Guo, Y.-R., Cao, Q.-D., Hong, Z.-S., Tan, Y.-Y., Chen, S.-D., Jin, H.-J., et al. (2020). The Origin, Transmission and Clinical Therapies on Coronavirus Disease 2019 (COVID-19) Outbreak – an Update on the Status. *Mil. Med. Res.* 7 (1), 11. doi:10.1186/s40779-020-00240-0
- Hu, Z., Liu, Y., Zhai, X., Dai, J., Jin, G., Wang, L., et al. (2013). New Loci Associated with Chronic Hepatitis B Virus Infection in Han Chinese. *Nat. Genet.* 45 (12), 1499–1503. doi:10.1038/ng.2809
- Huang, Y.-H., Liao, S.-F., Khor, S.-S., Lin, Y.-J., Chen, H.-Y., Chang, Y.-H., et al. (2020). Large-scale Genome-wide Association Study Identifies HLA Class II Variants Associated with Chronic HBV Infection: a Study from Taiwan Biobank. *Aliment. Pharmacol. Ther.* 52 (4), 682–691. doi:10.1111/apt.15887
- Ishii, T. (2020). Human Leukocyte Antigen (HLA) Class I Susceptible Alleles against COVID-19 Increase Both Infection and Severity Rate. *Cureus* 12 (12), e12239. doi:10.7759/cureus.12239
- Iturrieta-Zuazo, I., Rita, C. G., García-Soidán, A., de Malet Pintos-Fonseca, A., Alonso-Alarcón, N., Pariente-Rodríguez, R., et al. (2020). Possible Role of HLA Class-I Genotype in SARS-CoV-2 Infection and Progression: A Pilot Study in a Cohort of Covid-19 Spanish Patients. *Clin. Immunol.* 219, 108572. doi:10.1016/j.clim.2020.108572
- Jiang, D., Ma, X., Yu, H., Cao, G., Ding, D., Chen, H., et al. (2015). Genetic Variants in Five Novel Loci Including CFB and CD40 Predispose to Chronic Hepatitis B. *Hepatology* 62 (1), 118–128. doi:10.1002/hep.27794
- Kennedy, A. E., Ozbek, U., and Dorak, M. T. (2017). What Has GWAS Done for HLA and Disease Associations? *Int. J. Immunogenet.* 44 (5), 195–211. doi:10.1111/iji.12332
- Khera, A. V., Chaffin, M., Aragam, K. G., Haas, M. E., Roselli, C., Choi, S. H., et al. (2018). Genome-wide Polygenic Scores for Common Diseases Identify Individuals with Risk Equivalent to Monogenic Mutations. *Nat. Genet.* 50 (9), 1219–1224. doi:10.1038/s41588-018-0183-z
- Khor, S., Omae, Y., Nishida, N., Sugiyama, M., Kinoshita, N., Suzuki, T., et al. (2021). HLA-A*11:01:01:01, HLA-C*12:02:02:01-HLA-B*52:01:02:02, Age and Sex Are Associated with Severity of Japanese COVID-19 with Respiratory Failure. *Front. Immunol.* 12. doi:10.1101/2021.01.26.21250349
- Kosmicki, J. A., Horowitz, J. E., Banerjee, N., Lanche, R., Marcketta, A., Maxwell, E., et al. (2021). Pan-ancestry Exome-wide Association Analyses of COVID-19 Outcomes in 586,157 Individuals. *Am. J. Hum. Genet.* 108 (7), 1350–1355. doi:10.1016/j.ajhg.2021.05.017
- Kreutmair, S., Unger, S., Núñez, N. G., Ingelfinger, F., Alberti, C., De Feo, D., et al. (2021). Distinct Immunological Signatures Discriminate Severe COVID-19 from Non-SARS-CoV-2-driven Critical Pneumonia. *Immunity*, 1–16. doi:10.1016/j.immuni.2021.05.002
- La Porta, C. A. M., and Zapperi, S. (2020). Estimating the Binding of Sars-CoV-2 Peptides to HLA Class I in Human Subpopulations Using Artificial Neural Networks. *Cell Syst* 11 (4), 412–417. doi:10.1016/j.cels.2020.08.011
- Le Clerc, S., Limou, S., Coulonges, C., Carpentier, W., Dina, C., Taing, L., et al. (2009). Genomewide Association Study of a Rapid Progression Cohort Identifies New Susceptibility Alleles for AIDS (ANRS Genomewide Association Study 03). *J. Infect. Dis.* 200 (8), 1194–1201. doi:10.1086/605892
- Lee, M., Huang, Y., Chen, H., Khor, S., Chang, Y., Lin, Y., et al. (2018). Human Leukocyte Antigen Variants and Risk of Hepatocellular Carcinoma Modified by Hepatitis C Virus Genotypes: A Genome-wide Association Study. *Hepatology* 67 (2), 651–661. doi:10.1002/hep.29531
- Lenz, T. L., Spirin, V., Jordan, D. M., and Sunyaev, S. R. (2016). Excess of Deleterious Mutations Around HLA Genes Reveals Evolutionary Cost of Balancing Selection. *Mol. Biol. Evol.* 33 (10), 2555–2564. doi:10.1093/molbev/msw127
- Limou, S., Coulonges, C., Foglio, M., Heath, S., Diop, G., Leclerc, S., et al. (2008). Exploration of Associations between Phospholipase A2 Gene Family Polymorphisms and AIDS Progression Using the SNPlex™ Method. *Biomed. Pharmacother.* 62 (1), 31–40. doi:10.1016/j.biopha.2007.11.001
- Limou, S., Le Clerc, S., Coulonges, C., Carpentier, W., Dina, C., Delaneau, O., et al. (2009). Genomewide Association Study of an AIDS-Nonprogression Cohort Emphasizes the Role Played by HLA Genes (ANRS Genomewide Association Study 02). *J. Infect. Dis.* 199 (3), 419–426. doi:10.1086/596067
- Limou, S., and Zagury, J.-F. (2013). Immunogenetics: Genome-wide Association of Non-progressive HIV and Viral Load Control: HLA Genes and beyond. *Front. Immunol.* 4 (MAY), 1–13. doi:10.3389/fimmu.2013.00118
- Lin, M., Tseng, H.-K., Trejaut, J. A., Lee, H.-L., Loo, J.-H., Chu, C.-C., et al. (2003). Association of HLA Class I with Severe Acute Respiratory Syndrome Coronavirus Infection. *BMC Med. Genet.* 4 (1), 9. doi:10.1186/1471-2350-4-9
- Lorente, L., Martín, M. M., Franco, A., Barrios, Y., Cáceres, J. J., Solé-Violán, J., et al. HLA Genetic Polymorphisms and Prognosis of Patients with COVID-19. *Med Intensiva.* 2021;45(2):96–103. doi:10.1016/j.medin.2020.08.004
- MacArthur, J., Bowler, E., Cerezo, M., Gil, L., Hall, P., Hastings, E., et al. (2017). The New NHGRI-EBI Catalog of Published Genome-wide Association Studies (GWAS Catalog). *Nucleic Acids Res.* 45 (D1), D896–D901. doi:10.1093/nar/gkw1133
- Mayoral, E. P. C., Hernández-Huerta, M. T., Pérez-Campos Mayoral, L., Matias-Cervantes, C. A., Mayoral-Andrade, G., Barrios, L. Á. L., et al. (2020). Factors Related to Asymptomatic or Severe COVID-19 Infection. *Med. Hypotheses [Internet]* 144 (August), 110296. doi:10.1016/j.mehy.2020.110296
- Nguyen, A., David, J. K., Maden, S. K., Wood, M. A., Weeder, B. R., Nellore, A., et al. (2020). Human Leukocyte Antigen Susceptibility Map for SARS-CoV-2. *J. Virol.* 94 (13), 1–12. doi:10.1128/jvi.00510-20
- Nishida, N., Ohashi, J., Khor, S. S., Sugiyama, M., Tsuchiura, T., Sawai, H., et al. (2016). Understanding of HLA-Conferred Susceptibility to Chronic Hepatitis B Infection Requires HLA Genotyping-Based Association Analysis. *Sci. Rep.* 6 (April), 1–7. doi:10.1038/srep24767
- Novelli, A., Andreani, M., Biancolella, M., Liberatoscioli, L., Passarelli, C., Colona, V. L., et al. (2020). HLA Allele Frequencies and Susceptibility to COVID-19 in a Group of 99 Italian Patients. *HLA* 96 (5), 610–614. doi:10.1111/tan.14047
- Païro-Castineira, E., Clohisey, S., Klaric, L., Bretherick, A. D., Rawlik, K., Pasko, D., et al. (2020). Genetic Mechanisms of Critical Illness in Covid-19. *Nature* 591(7848), 92–98. doi:10.1038/s41586-020-03065-y
- Pelak, K., Goldstein, D. B., Walley, N. M., Fellay, J., Ge, D., Shianna, K. V., et al. (2010). Host Determinants of HIV-1 Control in African Americans. *J. Infect. Dis.* 201 (8), 1141–1149. doi:10.1086/651382
- Pisanti, S., Deelen, J., Gallina, A. M., Caputo, M., Citro, M., Abate, M., et al. (2020). Correlation of the Two Most Frequent HLA Haplotypes in the Italian

- Population to the Differential Regional Incidence of Covid-19. *J. Transl Med.* 18 (1), 1–16. doi:10.1186/s12967-020-02515-5
- Price, P., Witt, C., Allock, R., Sayer, D., Garlepp, M., Kok, C. C., et al. (1999). The Genetic Basis for the Association of the 8.1 Ancestral Haplotype (A1, B8, DR3) with Multiple Immunopathological Diseases. *Immunol. Rev.* 167 (1), 257–274. doi:10.1111/j.1600-065x.1999.tb01398.x
- Romero-López, J. P., Carnalla-Cortés, M., Pacheco-Olvera, D. L., Ocampo-Godínez, J. M., Oliva-Ramírez, J., Moreno-Manjón, J., et al. (2020). A Bioinformatic Prediction of Antigen Presentation from SARS-CoV-2 Spike Protein Revealed a Theoretical Correlation of HLA-Drb1*01 with COVID-19 Fatality in Mexican Population: An Ecological Approach. *J. Med. Virol.* 93 (4), 2029–2038. doi:10.1002/jmv.26561
- Roussel, M., Ferrant, J., Reizine, F., Le Gallou, S., Dulong, J., Carl, S., et al. (2021). Comparative Immune Profiling of Acute Respiratory Distress Syndrome Patients with or without SARS-CoV-2 Infection. *Cell Rep. Med* 2 (6), 100291. doi:10.1016/j.xcrm.2021.100291
- Ruan, Q., Yang, K., Wang, W., Jiang, L., and Song, J. Clinical Predictors of Mortality Due to COVID-19 Based on an Analysis of Data of 150 Patients from Wuhan, China. *Intensive Care Med.* [Internet]. 2020;46 (5):846–848. doi:10.1007/s00134-020-05991-x
- Rubicz, R., Yolken, R., Drigalenko, E., Carless, M. A., Dyer, T. D., Bauman, L., et al. (2013). A Genome-wide Integrative Genomic Study Localizes Genetic Factors Influencing Antibodies against Epstein-Barr Virus Nuclear Antigen 1 (EBNA-1). *Plos Genet.* 9 (1), e1003147. doi:10.1371/journal.pgen.1003147
- Sakuraba, A., Haider, H., and Sato, T. (2020). Population Difference in Allele Frequency of HLA-C*05 and its Correlation with COVID-19 Mortality. *Viruses* 12 (11), 1333. doi:10.3390/v12111333
- Sanchez-Mazas, A. (2020). A Review of HLA Allele and SNP Associations with Highly Prevalent Infectious Diseases in Human Populations. *Swiss Med. Wkly* [Internet] 150, w20214. doi:10.4414/smw.2020.20214
- Sanchez-Mazas, A. (2020). HLA Studies in the Context of Coronavirus Outbreaks. *Swiss Med. Wkly* 150, w20248. doi:10.4414/smw.2020.20248
- Sawai, H., Nishida, N., Khor, S-S., Honda, M., Sugiyama, M., Baba, N., et al. (2018). Genome-wide Association Study Identified New Susceptible Genetic Variants in HLA Class I Region for Hepatitis B Virus-Related Hepatocellular Carcinoma. *Sci. Rep.* 8 (1), 7958. doi:10.1038/s41598-018-26217-7
- Shachar, S. Ben., Barda, N., Manor, S., Israeli, S., Dagan, N., Carmi, S., et al. (2021). MHC Haplotyping of SARS-CoV-2 Patients: HLA Subtypes Are Not Associated with the Presence and Severity of COVID-19 in the Israeli Population. *J. Clin. Immunol.* doi:10.1007/s10875-021-01071-x
- Shi, Z., and Hu, Z. (2008). A Review of Studies on Animal Reservoirs of the SARS Coronavirus. *Virus Res.* 133 (1), 74–87. doi:10.1016/j.virusres.2007.03.012
- Spínola, H. (2016). HLA Loci and Respiratory Infectious Diseases. *J. Respir. Res.* 2 (3), 56–66. doi:10.17554/j.issn.2412-2424.2016.02.15
- Syangtan, G., Bista, S., Dawadi, P., Rayamajhee, B., Shrestha, L. B., Tuladhar, R., et al. (2021). Asymptomatic SARS-CoV-2 Carriers: A Systematic Review and Meta-Analysis. *Front. Public Heal* 8, 1–10. doi:10.3389/fpubh.2020.587374
- The Severe Covid-19 GWAS Group (2020). Genomewide Association Study of Severe Covid-19 with Respiratory Failure. *N. Engl. J. Med.* 383 (16), 1522–1534. doi:10.1056/NEJMoa2020283
- Thoens, C., Heinold, A., Lindemann, M., Horn, P. A., Chang, D-I., Scherbaum, N., et al. (2018). A Single-Nucleotide Polymorphism Upstream of the HLA-C Locus Is Associated with an Anti-hepatitis C Virus-Seronegative State in a High-Risk Exposed Cohort. *J. Infect. Dis.* 218 (12), 2016–2019. doi:10.1093/infdis/jiy492
- Tomita, Y., Ikeda, T., Sato, R., and Sakagami, T. (2020). Association between HLA Gene Polymorphisms and Mortality of COVID-19: An In Silico Analysis. *Immunity, Inflamm. Dis.* 8 (4), 684–694. doi:10.1002/iid3.358
- Toyoshima, Y., Nemoto, K., Matsumoto, S., Nakamura, Y., and Kiyotani, K. (2020). SARS-CoV-2 Genomic Variations Associated with Mortality Rate of COVID-19. *J. Hum. Genet.* 65 (12), 1075–1082. doi:10.1038/s10038-020-0808-9
- Trowsdale, J., and Knight, J. C. (2013). Major Histocompatibility Complex Genomics and Human Disease. *Annu. Rev. Genomics Hum. Genet.* [Internet] 14 (1), 301–323. doi:10.1146/annurev-genom-091212-153455
- Ursu, L., Calenic, B., Diculescu, M., Dima, A., and Constantinescu, I. (2020). HLA Alleles and KIR Genes in Romanian Patients with Chronic Hepatitis C. *J. Gastrointest. Liver Dis.* 29 (4), 595–601. doi:10.15403/jglid-2546
- Vergara, C., Thio, C. L., Johnson, E., Kral, A. H., O'Brien, T. R., Goedert, J. J., et al. (2019). Multi-Ancestry Genome-wide Association Study of Spontaneous Clearance of Hepatitis C Virus. *Gastroenterology* 156 (5), 1496–1507. doi:10.1053/j.gastro.2018.12.014
- Visscher, P. M., Wray, N. R., Zhang, Q., Sklar, P., McCarthy, M. I., Brown, M. A., et al. (2017). 10 Years of GWAS Discovery: Biology, Function, and Translation. *Am. J. Hum. Genet.* [Internet] 101 (1), 5–22. doi:10.1016/j.ajhg.2017.06.005
- Wang, F., Huang, S., Gao, R., Zhou, Y., Lai, C., Li, Z., et al. (2020). Initial Whole-Genome Sequencing and Analysis of the Host Genetic Contribution to COVID-19 Severity and Susceptibility. *Cell Discov* 6(1), 83. doi:10.1038/s41421-020-00231-4
- Wang, S-F., Chen, K-H., Chen, M., Li, W-Y., Chen, Y-J., Tsoo, C-H., et al. (2011). Human-Leukocyte Antigen Class I Cw 1502 and Class II DR 0301 Genotypes Are Associated with Resistance to Severe Acute Respiratory Syndrome (SARS) Infection. *Viral Immunol.* 24 (5), 421–426. doi:10.1089/vim.2011.0024
- Wang, W., Zhang, W., Zhang, J., He, J., and Zhu, F. (2020). Distribution of <sc>HLA</sc> Allele Frequencies in 82 Chinese Individuals with Coronavirus Disease-2019 (COVID-19). *HLA* 96 (2), 194–196. doi:10.1111/tan.13941
- Welter, D., MacArthur, J., Morales, J., Burdett, T., Hall, P., Junkins, H., et al. (2014). The NHGRI GWAS Catalog, a Curated Resource of SNP-Trait Associations. *Nucleic Acids Res.* 42 (D1), D1001–D1006. doi:10.1093/nar/gkt1229
- WHO (2021). WHO Coronavirus (COVID-19) Dashboard. Available from: <https://covid19.who.int/>.
- Xie, C., Yeo, Z. X., Wong, M., Piper, J., Long, T., Kirkness, E. F., et al. (2017). Fast and Accurate HLA Typing from Short-Read Next-Generation Sequence Data with xHLA. *Proc. Natl. Acad. Sci.* [Internet] 114 (30), 8059–8064. doi:10.1073/pnas.1707945114
- Yengo, C. K., Torimiro, J., Kowo, M., Lebon, P. A., Tiedeu, B. A., Luma, H., et al. (2020). Variation of HLA Class I (-A and -C) Genes in Individuals Infected with Hepatitis B or Hepatitis C Virus in Cameroon. *Heliyon* 6 (10), e05232. doi:10.1016/j.heliyon.2020.e05232
- Yung, Y., Cheng, C., Chan, H., Xia, J. T., Lau, K., Wong, R. S. M., et al. (2020). Association of HLA-B22 Serotype with SARS-CoV -2 Susceptibility in Hong Kong Chinese Patients. *Hla*, tan.14135.
- Zahn, L. M. (2020). HLA Genetics and COVID-19. *Science* 368 (6493), 841–2841. doi:10.1126/science.368.6493.841-b
- Zhang, Q., Bastard, P., Liu, Z., Le Pen, J., Moncada-Velez, M., Chen, J., et al. (2020). Inborn Errors of Type I IFN Immunity in Patients with Life-Threatening COVID-19. *Science* 370 (6515), eabd4570. doi:10.1126/science.abd4570
- Zhang, S-Y., Zhang, Q., Casanova, J-L., and Su, H. C. (2020). Severe COVID-19 in the Young and Healthy: Monogenic Inborn Errors of Immunity? *Nat. Rev. Immunol.* 20 (8), 455–456. doi:10.1038/s41577-020-0373-7
- Zheng, X., Shen, J., Cox, C., Wakefield, J. C., Ehm, M. G., Nelson, M. R., et al. (2014). HIBAG - HLA Genotype Imputation with Attribute Bagging. *Pharmacogenomics J.* 14 (2), 192–200. doi:10.1038/tpj.2013.18
- Zhou, Y., Fu, B., Zheng, X., Wang, D., Zhao, C., Qi, Y., et al. (2020). Pathogenic T-Cells and Inflammatory Monocytes Incite Inflammatory Storms in Severe COVID-19 Patients. *Natl. Sci. Rev.* 7 (6), 998–1002. doi:10.1093/nsr/nwaa041
- Zhu, N., Zhang, D., Wang, W., Li, X., Yang, B., Song, J., et al. (2020). A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N. Engl. J. Med.* 382 (8), 727–733. doi:10.1056/nejmoa2001017
- Zmijewski, J. W., and Pittet, J-F. (2020). Human Leukocyte Antigen-DR Deficiency and Immunosuppression-Related End-Organ Failure in SARS-CoV2 Infection. *Anesth. Analg* 131 (4), 989–992. doi:10.1213/ane.0000000000005140

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