Title: Gene influencing in COVID-19 infection, disease severity and its Pharmacotherapy

Running title: Gene and COVID-19 infection

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Abstract

COVID-19 pandemic has badly affected the world, having fatality rate ranging from 1 to 10% that differs in various countries. The median time from symptoms to clinical recovery is 6–8 weeks and to death is 2 to 8 weeks. Severity of disease and increasing mortality in COVID 19 is primarily due to presence of comorbidities like cardiovascular disease, pre-existing lungs disease, hypertension, diabetes, obesity and cancer. It is already known to us that humans show difference in drug responses because of their varied genetic make-up. Population genomics furnish an insight about genetic characteristic of a populations and it is critical in determining susceptibility, severity and natural protection against infectious diseases. Therefore, understanding the population genetic makeup may be deemed necessary to identify those who are at risk or protective from disease and develop genomics information, that would be useful in providing insight about COVID−19 disease severity or outcomes. Some of the proposed genetic gateways in COVID 19 pathogenesis are mentioned in this review including roles of ACE2 gene, HLA gene, Chromosome 3P21.31, ABO locus, genes responsible for cytokine storm, TLR-pathway, Family Mediterranean fever and G6PD deficiency. Significant interindividual variability in response to drug therapy exists in patients. This review also evaluates the current therapeutics in COVID-19 like hydroxycholoroquine, azithromycin, RNA polymerase inhibitors, interleukin inhibitors, antivirals, ivermectin, doxycyclin and their pharmacogenomics viewpoint. Such Pharmacogenomic studies are very helpful for the physicians to choose and give accurate first line therapy for COVID 19 patients.

Keywords

COVID 19, Pharmacogenomics, Population genomics, Genetic gateways, cytokine storm, Therapeutics in COVID-19

Introduction

Currently, the world is badly hit by COVID-19 pandemic. The case fatality rate of COVID-19 ranging from 1 to 10% that differs in various countries[1]. This variation may be due to unknown population size, frequency and accuracy of testing, proper maintaining of registry, demographic parameters of population and capacity of healthcare systems. The pathogenesis of COVID-19 can be broadly classified into four stages - Stage 1 being pre or asymptomatic phase that lasts for few days. Stage 2 is defined by symptoms of fever, cough, malaise, may progress to viral pneumonia with high viral load (within span of 5 days) or improve gradually with development of antibodies around 7 to 10 days. A very small fraction of patients may progress to stage 3, develop the symptoms of cytokine release syndrome with high levels of pro-inflammatory cytokines and other host markers of inflammation (like CRP, ferritin, D-dimers, LDH etc.), lymphopenia and respiratory failure. This ultimately proceeds to Stage 4 which is acute respiratory distress syndrome (ARDS) and multi-organ involvement, seen in 60-70% of patients admitted to ICU[2]. The median time from symptoms to clinical recovery is 6–8 weeks and to death is 2 to 8 weeks.

Disease severity and increasing mortality in COVID 19 is primarily due to presence of comorbidities like cardiovascular disease, pre-existing lungs disease, hypertension, diabetes, obesity and cancer. Elderly population are mostly affected, though younger patients

are also suffering from acute conditions and dying due to this COVID-19. Even children were initially thought to be protected from severe disease conditions but Kawasaki disease and vasculitis type of acute inflammatory response[3] have been noted in them. Therefore, the question rises here - can there be a genetic predilection for this pandemic COVID-19?

It is already known to us that humans show difference in drug responses because of their varied genetic make-up. This is because, drug metabolism, its efficacy and adverse effects is determined by genetic makeup of the individual. The concept of pharmacogenetics and pharmacogenomics is well established already. *Pharmacogenetics refers to the study of DNA sequence variation as it relates to differential drug response in individuals, i.e. the use of genomics to determine an individual's response. Pharmacogenomics refers to the use of DNA-based genotyping in order to target pharmaceutical agents to specific patient populations in the design of drugs[4].*

Since COVID 19 has no definite treatment till now, many drugs are being repurposed and used or are under investigation for use in this disease. Some studies already suggested that genetic makeup interplay the lack of efficacy and fatal side effects of hydroxychloroquine in treatment of COVID 19[5]. Pharmacogenomics is very helpful for the physicians to choose and give accurate first line therapy in critically ill patients, where ineffective therapy could be life threatening for them. Other factors that influences the efficacy and toxicity of drugs used in COVID 19 could be irrational prescribing, polypharmacy, drug interactions, which needs to be evaluated further.

This review focuses on how genetic make-up of the individual are influencing in the pathogenesis and therapeutic outcome of COVID-19.

Individuals Genetic Makeup vis a vis Covid-19 Infection and Severity

Population genomics furnish an insight about genetic characteristic of a populations and it is critical in determining susceptibility, severity and natural protection against infectious diseases. Therefore, understanding the population genetic makeup may be deemed necessary to identify those who are at risk or protective from disease and develop genomics information, that would be useful in providing acumen about COVID−19 disease severity or outcomes[6].

Unfortunately, there are no genetic data available in terms of topographical variation of COVID−19 severity or outcome worldwide. The researchers have already identified few genes associated with the immune system's, as well as a protein that allows the coronavirus into our cells, those are related to COVID-19 susceptibility as well as severity. Some proposed genetic data are given below -

1. Role of angiotensin - converting enzyme 2 (ACE 2) gene

ACE2 is important in maintaining homeostasis and balance of the renin−angiotensin system, vascular function, and cardiovascular complications. The most frequent comorbidity found with COVID−19 are hypertension and diabetes, and both these conditions are modulated by ACE2. It has now become established that SARS−CoV−2 uses angiotensin−converting enzyme 2 (like SARS−CoV) to enter into the host cell and the expression of

ACE2 influences SARS−CoV infection[7,8]. The ACE2 gene located in X chromosome (Xp22.2); encodes the angiotensin-converting enzyme-2[9]. The transcriptional activity of ACE2 gene become altered among functional variants of ACE2 gene. The types of single nucleotide polymorphisms (SNPs) of the ACE2 gene varies among different populations[10]. Multiple studies confirmed that at least 9 human ACE2 variants (i.e., S19P, I21V, E23K, K26R, T27A, N64K, T92I, Q102P and H378R) are more susceptible to viral binding, whereas another 17 variants of ACE2 (i.e., K31R, N33I, H34R, E35K, E37K, D38V, Y50F, N51S, M62V, K68E, F72V, Y83H, G326E, G352V, D355 N, Q388L and D509Y) are protective against viral entry due to lower binding propensity to SARS-CoV-2 spike protein (receptor-binding domain)[11].

The protective variants of K31R and Y83H of ACE2 gene has been found at relatively higher frequency among Asian populations than global average. Whereas the frequency of T92I, a risk variant allele is relatively more in European as compared to a global average and another risk variant K26R mutation is often seen among Caucasians[12].

Studies demonstrated that ACE-2 has critical role in inflammatory processes. Genetic deficiency of ACE2 up regulates the production of cytokines (interleukins, interferons, chemokines) and induces vascular inflammation in ACE-2 knockout (KO), apolipoprotein E (ApoE) KO and ApoE/Ace2 double KO mice model[13,14]. Study also demonstrate the ACE-2 expression is associated with various immune signatures like markers of natural killer cells (NK cells), T lymphocyte, B lymphocyte and host's interferon response[15]. All above conclusion goes in favour that ACE2 is also involved in post−infection downstream inflammatory responses apart from receptor for SARS−CoV−2.

2. Role of HLA gene (and antigen presentation) in inducing protective immunity against COVID-19

The human leukocyte antigen (HLA) molecules are human version of the major histocompatibility complex (MHC), a group of genes that are present in many species. Human MHC complex consists of more than 200 closes together genes located on chromosome 6. HLA system is an important immune regulatory component that differentiate self and non-self-antigens and a primary agent in conferring adaptive immunity against infectious diseases. Several thousand of polymorphisms has identified in HLA genes, so HLA exhibit extreme diversity. And this genetic diversity at HLA genes is responsible for inter individual difference in immune response against pathogens[16].

MHC molecules acts as a receptor for antigens from pathogens. The peptide binding groove of the MHC class I molecules, bound to a viral antigenic peptide and then present the peptides to the virus- specific cytotoxic T lymphocytes (CD8+ T cells). Structural variation of the peptide binding grooves (essential for binding to various peptides) are determined by variations within MHC class I genes[17]. So, HLA genes are critical in MHC- peptide interactions, which determines the susceptibilities and immune responses to viral infection.

A study on severe COVID-19 patients with respiratory failure, exhibit extremely low HLA-DR expression along with significant decrease in CD4 lymphocytes, CD19

lymphocytes, and natural killer (NK) cells count, might indicating the immune-regulatory/response role of HLA in COVID-19[18]. An in-silico analysis on genetic variability of binding affinity of MHC class I molecules with all the peptides of SARS-CoV-2, covering 145 HLA-A, -B, and -C genotypes showed that the HLA-B*46:01[19] allele could increase susceptibility to COVID-19, as this allele displayed fewest presenting/binding sites for SARS-CoV-2 peptides. Whereas HLA-B*15:03[20] could provide CD8+ T cell based protective immunity, as this allele had highest potency to present SARS-CoV-2 peptides to CD8+ T cell. And at haplotype level, HLA-A*02:02[21], HLA-B*15:03, and HLA-C*12:03[22] showed highest and HLA-A*25:01, HLA-B*46:01, and HLA-C*01:02 exhibited lowest number of predicted representation sites for epitopes from SARS-CoV-2 to CD8+ T cell. So, population contain later HLA sets are more susceptible to SARS-CoV-2 infection[23].

The topographical pattern/variation in the incidence of COVID-19 infection, severity and mortality indicating towards the population-specific HLA alleles may be a most critical determinant of protective immune response against SARS-CoV-2 and ascertain the resistant or vulnerability to COVID-19 in individual or population[24]. For example, a recent study showed HLA-A*02 alleles (like A*02:01, *02:03, *02:05, *02:06, *02:07, and *02:11) have a higher frequency among North and central Indian populations, among these A*02:11 display highest occurrence at the repertoire level, and Indian populations are fortunate to have this allele commonly, whereas Caucasian and oriental populations have completely lack of this allele[25]. As mentioned above HLA-B*46:01 allele that could related to increase susceptibility to COVID-19, is seen among people of South East Asian descent. But completely absent in Indian and African populations and rarely present in European populations, which make these population natural resistant to COVID-19[26].

Studies already have concluded that olfactory dysfunction is one of the clinical presentations of mild to moderate COVID-19[27,28,29]. It is a well-established fact HLA gene are inherent in olfaction[30,31], and olfactory receptor (OR) gene are seeming to be MHC-linked with existing polymorphisms[32,33]. Though the relationship between HLA polymorphism and olfactory dysfunction has not been studied in COVID-19 yet, but it may impart an insight in HLA related pathogenesis of disease further.

3. Gene responsible for the cytokine storm

The most demanding clinical debate worldwide at present is why there are individual variability in developing cytokine storm, and this already have increased the interest in identifying underpinning genetic mechanisms[34]. Cytokine production is a natural immunological event and T lymphocytes are most important producers of cytokines, which is regulated by genetic as well as epigenetic processes[35]. Genetic polymorphisms of the cytokine genes are related to the production of inappropriate amount cytokines, which imparts the natural susceptibility, severity or protection to infectious diseases[36].

Studies already established that, the cytokine gene polymorphism pattern is influenced by ethnicity[37]. Till now no research has been done on cytokine gene polymorphisms and the risk of cytokine storm in COVID-19, but several studies have concluded the associations between cytokine gene polymorphisms like IFN-γ +874A allele[38]

(low IFN-γ expression), IL12RB1[39] and susceptibility to SARS-CoV infection. A meta-analysis suggests the presence of IL6 174C allele is associated with higher IL-6 production and pneumonia severity[40].

Future research for identification of relation between various pro-inflammatory cytokine genes polymorphism and cytokine storm in SARS-CoV2 infection can certainly provide further insights on the COVID-19 pandemic.

4. Chromosome 3P21.31 and COVID-19

Studies concluded that among the cluster of six genes (SLC6A20, LZTFL1, CCR9, FYCO1, CXCR6, and XCR1), on chromosome 3p21.31 locus several is involved in Covid-19 susceptibility and severity. For example, SLC6A20, that encodes the sodium–imino acid (proline) transporter 1 (SIT1), which functionally connected with angiotensin-converting enzyme 2, the SARS-CoV-2 receptor[41,42]. CC motif chemokine receptor 9 (CCR9) and the C-X-C motif chemokine receptor 6 (CXCR6) regulates the lung-resident memory CD8 T cells during immune response against respiratory pathogens, including viruses[43]. The risk allele rs11385942-GA is associated with decreased CXCR6 expression and increased expression of SLC6A20, and LZTFL1 in human lung cells. It was found that risk allele 3p21.31 (rs11385942) was present in higher frequencies among patients received mechanical ventilation. Even younger patients who carry homozygous risk allele frequently suffered from severe disease and received mechanical ventilation tan heterozygous or carrying non-risk allele[44].

5. ABO locus and COVID-19

Diversity of the ABO gene located on chromosome 9q34.2 is the fundamental of the ABO (blood group) system, i.e. individual carrying a particular allele determines the blood group of that individual. The association between ABO locus and susceptibility for COVID-19 has been established (as susceptibility to SARS-CoV-1 infection[45]) by genome-wide association study as well as nongenetic studies[46,47].

In a meta-analysis corrected for age and sex, confirmed that blood group O is associated with a significant lower risk of acquiring Covid-19 than that of non-O blood groups, whereas blood group A was associated with a higher risk than non-A blood groups (Details are provided in Supplementary Appendix 8, available at NEJM.org)[44], but interestingly no significant difference has been found in blood-group distribution among patients received supplemental oxygen or mechanical ventilation[44].

The possible biologic mechanisms of these findings may be due to presence of neutralizing antibodies against protein-linked N-glycans[48] (Coronavirus S protein trimers are covered by an extensive glycan shield, that is made of N-linked glycans and surrounds the receptor-binding domain. The presence of anti-A and anti-B antibodies in individuals with blood group O could prevent infection by blocking virus attachment and entry)[49] or other biologic effects of the detected variant[50,51,52], including von Willebrand factor stabilization[53,54]

6. TLR-gene in SARSCoV-2 infection

Toll-like receptors (TLRs) are one of the several type of pattern recognitions receptors (PRRs), which are capable to recognize molecules expressed on pathogens (the so-called Pathogen-Associated Molecular Patterns or PAMPs), or damaged cells (the Damage-Associated Molecular Patterns or DAMPs) and initiate the inflammation and/or innate immune response soon after a challenge by pathogens including SARS-CoV-2. TLR signalling is crucial in the regulation of cytokine expression during protective host immune response[55,56]; and also, might have critical role in inducing cytokine storm in SARS-CoV-2 infection.

It is now well established that the functional diversity of TLR molecules are also governed by genetic variation among TLR genes. The identified 10 TLR genes are expressed on five different chromosomes. TLR1, TLR6 and TLR10 are located on chromosome 4, TLR7 and TLR8 are located on the X chromosome, TLR5 on chromosome 1, TLR9 on chromosome 3, TLR2 and TLR3 on chromosome 4 and TLR4 on chromosome 9[57].

Currently, there are no studies on the role of TLR pathway in SARS-CoV-2 infection, but Previous animal studies had demonstrated that TLR3, TLR3/TLR4 adaptor TRIF (Toll/IL-1R domain-containing adaptor inducing IFN) and Ticam2 (Toll Like Receptor Adaptor Molecule 2) deficient mice are more susceptible to SARS-CoV infection as well as alterations in natural inflammation[58,59]. The researchers (Radboud University Medical Center, Netherlands) found that rare loss-of-function mutation of X-chromosomal TLR7 were associated with impaired type I and II IFN responses and associated with primary immune deficiency among young COVID-19 patients. Though no association between TLR7 function and inborn error of immunity has been identified till now, but the critical role TLR7 for protection from coronavirus is well known now.

The interesting fact is that, the TLR genes display a unique distribution pattern in various ethnic populations and also are the target of selection pressure. The critical role of TLR genes in determining different susceptibility and severity to SARS-CoV-2 infection needs to be tested further in detail.

7. Complement system and SARS-CoV-2 infection

The complement system is comprising of over 30 proteins; their activation and function is taking place in an organized manner by 3 activation pathways named as the classical, the lectin, and the alternative pathway. All these pathways converge to a central component by activating C3 (by enzyme complexes—the classical/lectin (C4bC2a) and the alternative C3 convertases), which ultimately activate the downstream i.e. C3a, C4a, C3b, C4b and membrane-attack complex (MAC or C5b-9 complex). The function of complement system is to eliminate pathogens (including viral infections)[60] through opsonization, attract and activate neutrophils and macrophages, intensify humoral immunity and cell mediated response[61], but uncontrolled activation may result in exaggerated acute or chronic inflammation, tissue injury, and the activation of coagulation. So, complement is a double-edged sword of our immune system. Complement system also interact with TLRs and further activate the inflammatory immune cells, especially Th17 cells[62].

An animal study demonstrates SARS-CoV-infected C3−/− mice had less respiratory dysfunction and low levels of cytokines and chemokines response in the serum as well as lungs[63]. In addition, complement system hyper-activation (mediated by mannose-binding protein-associated serine protease 2 or MASP-2 and exaggerated by highly pathogenic coronavirus N protein) and lung injury was found among severe COVID-19 patients[64]. This suggests that complement components have important implications in the induction of the cytokine storm and inflammation in SARS-CoV-2 infection.

Complement genes polymorphisms has identified to be associated with multiple diseases, including various infectious diseases. For example, loss of function single nucleotide polymorphisms (SNPs) in complement factors, such as C5 (rs17611) and C3 (rs2230199), can increase the risk of bacterial infection, autoimmune disease (like systemic lupus erythematosus) and malignancies[65]. But till now there are no data available on complement gene polymorphism and risk and severity of SARSCoV-2 infection. Apart from functional variance of genes encoding TLR and cytokine, genes determining the function of the complement system also could furnish an insight about the immensity of inflammatory responses (cytokine storm) in COVID-19.

8. Familial Mediterranean fever (FMF)

FMF is an autosomal recessive, monogenic, autoinflammatory hereditary fever syndrome that was first described in Mediterranean populations (also affecting Jewish[66], Turkish, Armenian, North Africans and those of Arabic descent)[67]. It is characterized by short, recurrent bouts of fever that last 12–72 h, with raised inflammatory markers (TNF alpha, IL1 and IL 6), polyserositis and dermal manifestations[68].

MEFV gene on chromosome 16p13.3 encodes a protein named pyrin (also called marenostrin or TRIM20) an important modulator of innate immunity like clustering of inflammasome. In response to intracellular threats, inflammasome activates inflammatory mediators and regulators of innate immunity[69]. Gain-of-function mutations of MEFV gene are, producing clinically heterogeneous phenotypes with variation of pyrin functions, for example it may intensify the inflammasome sensitivity and delay resolving of innate immune responses. So, mutations in MEFV may be associated with cytokine storm in COVID-19. For instance, MEFV mutations have been reported among Jewish, Japanese[70], Spanish[71] and Iranian[72] populations.

Colchicine or tocilizumab is used to treat FMF to reduce the severity, duration and complication of disease, and these two medicines are being investigated/used in adult patients diagnosed with COVID 19 infection[73,74,75] Further genetic research may provide more insight about relation between MEFV gene and COVID-19.

9. G6PD deficiency

G6PD deficiency (X linked dominant polymorphisms) increase the oxidative stresses of the cells. G6PD is the rate limiting enzyme in the pentose phosphate pathway and produce NADPH, that maintain the balance of reduced glutathione (GSH) and oxidized glutathione

(GSSG) in cells. Glutathione is the physiological anti-oxidant that protect cells against oxidative stress[76].

The insight of G6PD deficiency may interplay with severe COVID-19 infections, come from several observations like – (1) males predominantly suffered from severe disease (2) previous documentation of susceptibility to a common alpha coronavirus (229E) infection in G6PD deficient cells (3) G6PD deficiency reduces the production of IL10 and other anti-inflammatory cytokines but increases IL6 and other pro-inflammatory cytokines among patient experienced severe trauma[77]. (4) animal experiments demonstrate that G6PD deficiency intensify the cytokine responses and cause hyperinflammation (mostly increased IL1β, IL6, and IL10 levels) following acute endotoxemia[78]. More detail research may establish the association between G6PD deficiency and COVID-19 further.

G6PD deficiency affects around 400 million people, distributed globally, especially in (current or previous malaria endemic areas likely due to evolutionary advantage against malaria) blacks from Africa and America (lowest prevalence, 12%) sub Saharan Africa or Brazil, Sardinia, Greece, Kurdish Jews (highest prevalence, up to 70%), South China, Thailand and India[79]. Topographical distribution data of COVID-19 infection and G6PD deficiency may also strengthen above observations.

Pharmacogenomic considerations of COVID-19 therapies

Significant interindividual variability in response to drug therapy exists in patients. Genetic diversity can affect the disposition (pharmacokinetic), efficacy, tolerability and safety (pharmacodynamics) of a drug. Such interindividual variability can be managed successfully by pharmacogenomics knowledge to obtain the best desired therapeutic outcome and least adverse drug reaction. It is noteworthy that pharmacogenomics data are now being included to drug labels, intended to facilitate the selection of appropriate drug or adjusting the dose to an individual patient to optimize therapeutic outcome. In this subsequent part we will discuss the current therapeutics in COVID-19 and their pharmacogenomics viewpoint.

Hydroxychloroquine

Hydroxychloroquine (HCQ), a derivative of the antimalarial drug chloroquine, is mainly indicated as an immunomodulatory agent in the management of systemic lupus erythematosus and rheumatoid arthritis. It was repurposed for the treatment of Covid-19 based on previously conducted in-vitro and animal studies which showed antiviral activity of chloroquine against influenza, chikungunya, SARS-CoV-1 and seasonal infections caused by other corona viruses[80,81,82,83]. Since the SARS-CoV-2 follows a similar process of pH-dependent internalization (by endocytosis and lysosomal fusion) for entry into host cell and further replication, as the above viruses, it was thought that HCQ would also prove beneficial in treating Covid-19 and was quickly adopted for clinical use. Subsequently, preliminary results from the Solidarity trial (including the French Discovery trial data) and the UK's Recovery trial failed to show any significant reduction in mortality with HCQ when compared to standard of care. It rapidly fell into disrepute and was withdrawn from most national treatment guidelines and also discontinued as a treatment arm in the WHO Solidarity trial[84,85]. The Government of India guidelines, in contrast, continues to recommend use of

HCQ in selected patients with mild symptoms having high risk features, and in moderate cases of hospitalized COVID-19 patients. The ICMR also recommends the use of HCQ for prophylaxis in frontline workers based on encouraging results from a case-controlled study[86].

The metabolism of both chloroquine and hydroxychloroquine occurs with the help of the microsomal cytochrome P450 enzymes CYP2D6, CYP2C8 and CYP3A4, all of which are known to exhibit genetic polymorphisms. Several allelic variations in CYP2D6 have been reported in man leading to differing phenotypes such as poor metabolisers (CYP2D6*4), intermediate metabolisers (CYP2D6*10), extensive metabolisers (CYP2D6*2) and ultrarapid metabolisers[87]. Studies have also reported distinct ethnic variations in the frequency of occurrence of such polymorphisms[88,89]. Although studies in the Indian population are limited, research has found CYP2D6*2 allele to be the most frequent variant in the Gujarati (47%) and South Indian populations (34.8%). The Gujarati population (13%) were also found to exhibit high levels of CYP2D6*4 along with the Punjabi population (24%), while the Bengali population (21%) were found to have high levels of CYP2D6*10[90]. Thus, the pharmacokinetics of chloroquine and hydroxychloroquine may vary greatly among different ethnic groups, which may have an implication on their safety and efficacy. Interestingly, both these drugs are also known to inhibit CYP2D6, which should be kept in mind when drugs like ondansetron, haloperidol, etc, which are CYP2D6 substrates with a propensity to prolong QT interval, are prescribed concomitantly. On the other hand, the effectiveness of drugs like codeine and tramadol, which are prodrugs requiring activation by CYP2D6, may be compromised when co-prescribed with chloroquine or hydroxychloroquine.

Apart from the risk of QT prolongation, both these drugs are also known to cause retinopathy with high doses or on prolonged usage. Retinopathy has been found to be less frequent in individuals who possess the minor allele of ABCA4[91].

Azithromycin

Based on the results of an observational study, it was suggested that combined therapy of azithromycin and hydroxychloroquine was more effective in COVID-19 than hydroxychloroquine alone[92]. Although azithromycin causes lesser drug-drug interactions than other macrolide agents, co-therapy with hydroxychloroquine may increase the risk of prolonged QT interval leading to fatal arrhythmias[93]. Individuals with 2677GG (rs2032582) and 3435CC (rs1045642) diplotypes in ABCB1 (P-glycoprotein) gene have been seen to attain higher maximum plasma concentration of azithromycin than those with 2677TT/3435TT diplotypes[94]. So, efficacy and drug interaction of varies with genetic polymorphism.

RNA Polymerase inhibitors

The nucleotide analogues, remdesivir, favipiravir and ribavirin have been used to treat COVID-19. All these agents are converted to their active forms by various intracellular enzymes and later inhibit viral RNA polymerase to exert their anti-viral effect.

Remdesivir has been approved for restricted emergency use as a treatment option for COVID-19 by the DCGI on the basis of favourable risk-benefit ratio in randomized, double-

blinded, placebo-controlled trials[95]. The uptake and metabolism of remdesivir depends on P-glycoprotein and OATP1B1 transporters, and CYP2C8, CYP2D6, and CYP3A4 enzymes respectively[96]. Although there is a dearth of data on the pharmacogenomics of remdesivir, polymorphisms of the genes coding for the above transporters and metabolizing enzymes may affect its pharmacokinetics and hence drug response in terms of desired outcome, adverse drug reaction and drug interactions[97].

The DCGI has also approved **favipiravir** for "restricted emergency use" in mild to moderate cases of COVID-19[98]. Although no pharmacogenomic data on favipiravir is available, there is a theoretical possibility that since it is metabolized by aldehyde oxidase and also xanthine oxidase, to some extent, variations of these enzymes in different individuals may affect the pharmacokinetics of this drug[99]. Though not studied separately, there are certain theoretical possibilities that effectiveness of flavipiravir is depends on polymorphism (SNPs) of metabolizing enzyme - aldehyde oxidase. Fast metabolizers (FMs) (hAOX1-N1135S and hAOX1-H1297R, 2- to 4-fold increased catalytic efficiency) usually may have poor response to flavipiravir whereas, poor metabolizers (PMs) (hAOX1-R802C and hAOX1-R921H, 2.4- to 1.5-fold reduced activity) may exhibits drug toxicity[100].

Ribavirin, a drug used for hepatitis C, has also been considered in the treatment of COVID-19 and is being taken up in various research studies as a treatment modality. The trough concentrations of ribavirin are known to differ greatly in the presence of polymorphic variants of the influx transporters SLC29A1, SLC28A2 and SLC28A3, with significantly higher trough concentrations achieved in those with SLC29A1 variant[101]. Also, individuals with ITPA (inosine triphosphatase) variants with decreased activity in red blood cells are less prone to the hemolytic side effect of ribavirin[102,103].

Interferon (INF) β-1b

IFN-β1b, which was found to be effective in the treatment of SARS and MERS is also being explored as a potential therapy for COVID-19 as monotherapy and also in combination with other drugs like lopinavir/ritonavir[104]. In a study of patients of multiple sclerosis treated with IFN-β1b, patients with variants of IRF6 were found to be at a higher risk of drug-induced liver damage[105]. In another cohort study of IFN-β1b-treated multiple sclerosis patients, those with HLA-DRB1*15 were found to be at a lower risk of developing biologically significant levels neutralizing antibody than those having the HLA-DRB1*04 allele[106].

Antiretrovirals

Lopinavir and ritonavir combination was among the first drugs which were considered for the management of COVID-19[107]. Both these drugs are metabolized by CYP3A4 and CYP3A5 enzymes, and therefore polymorphic variations in their encoding genes may lead to differences in their pharmacokinetics[108]. In the all clinical situation lopinavir and ritonavir are always used in combination, and study shows CYP3A5 genetic polymorphism had no effect on the trough plasma concentrations of these drugs[109].

The plasma concentration of **darunavir** depends on the influx transporters SLCO1A2, SLCO1B1, and on efflux transporters like MRP1[110]. Study demonstrate that those

having SLCO3A1 rs8027174 GT/TT genotypes had a lower clearance of darunavir, while a 2.5 times higher central volume of distribution was seen in those who were homozygous for rs4294800 A allele[110].

Interleukin inhibitors (Tocilizumab, Sarilumab, Anakinra, Siltuximab)

Since interleukins, mainly IL-6, play a major role in the development of the cytokine storm, interleukin inhibitors are being used to manage severe cases[111].

Tocilizumab (TCZ) is a monoclonal antibody which binds to both membrane-bound and soluble IL-6 receptors. In a study conducted on patients of rheumatoid arthritis receiving tocilizumab, single-nucleotide polymorphisms rs12083537, rs2228145, and rs4329505 were seen to be associated with clinical response, of which presence of the major allele (A) of rs12083537 and the minor allele (C) of rs4329505 were found to show poor response with regards to swollen joint count[112,113]. Polymorphisms in the UGT1A1 gene are strongly associated with increased levels of unconjugated bilirubin levels in patients during tocilizumab therapy. The rs6742078 TT genotype is at a risk of attaining higher levels of unconjugated bilirubin[114].

Sarilumab also binds to both membrane-bound and soluble IL-6Rα to exert its anti-IL6 action. Genetic variations in the UGT1A1 gene may also be responsible for the rise in bilirubin levels during therapy with sarilumab[115].

Anakinra competitively inhibits IL-1 from binding to its cell membrane receptor, thus blocking cell signaling. Literature search on the pharmacogenomics of anakinra revealed only one study which showed that the presence of the rarer T allele at IL-1α (+4845) was associated with clinical response to treatment[116].

Janus kinase inhibitors (ruxolitinib, baricitinib)

These drugs are also being explored as potential agents in COVID-19 therapy due to their immunomodulatory action. Although the pharmacogenomics of these two drugs have not been studied yet, the fact that both ruxolitinib and baritinib are substrates of CYP3A4 suggests a theoretical possibility of differences in their activity in individuals with different variants of CYP3A4[117]. Additionally, the uptake of baricitinib depends on the OAT3 transporter which is encoded by SLC22A8, the pharmacogenomics of which have been studied in a different substrate drug[118,119].

Corticosteroids

Corticosteroids being potent immunosuppressants are the mainstay of management of ARDS and lung damage associated with severe Covid-19[120]. The results of several research studies on the pharmacogenomics of corticosteroids have found that there is increased response to these drugs in individuals with CRHR1 (rs1876828), T gene (rs3127412 and rs6456042), TBX21 gene (rs2240017) and ORMDL3 (rs2872507). On the other hand, those with FCER2 (rs28364072), ST13 (rs138335 and sr138337) and GLCCI1 (rs37972) were found to show decreased response to corticosteroids[121]. No specific pharmacogenetic information on the effectiveness of corticosteroids for ARDS was found.

Ivermectin

Although data on the effectiveness of this combination in Covid-19 patients is limited, it is now being recommended by some authorities in treatment as well as prophylaxis of COVID-19. Ivermectin is a known substrate for both the MDR1 and the CYP3A4 which probably act synergistically and determining its pharmacokinetics[122]. The MDR1 gene polymorphism is often associated with a decrease in P-gp expression or its activity, thereby affect the absorption and tissue concentrations of ivermectin and other substrates of MDR-1[123]. The CYP3A4*1B variant allele, associated with the decrease of CYP3A4 activity, was detected in 69-82% African and 4-9% Caucasian population but has not been detected in the Asian population[124]. The CYP3A4*3 variant was reported in only 2% of Caucasian populations[124]. Individual carrying above variants have better ivermectin absorption. Genetic polymorphism also determining the ivermectin toxicity. Studies conducted in dogs have found that ABCB-1 polymorphisms which lead to loss of p-glycoprotein function results in neurotoxicity and fatal toxicosis[125]. Since ABCB-1 is also responsible for efflux transport of ivermectin in man, further studies on the pharmacogenomics of ivermectin are warranted in humans.

Siltuximab

Siltuximab is a monoclonal antibody that directly neutralizes interleukin (IL)-6, an inflammatory cytokine detected at elevated levels in multiple inflammatory conditions, including COVID-19. It specifically binds to IL-6, thereby inactivating IL-6 induced signalling. Siltuximab exerts its actions through activation of Stat3 downstream antiapoptotic regulatory genes *BcL-XL, MCL-1* and survivin. Genetic polymorphisms may result in inhibition of Stat3 phosphorylation and those gene expressions results in reduce therapeutic potential of liver cancers[126].

Doxycycline

Doxycycline is an antimicrobial agent but also possess antiviral as well as anti-inflammatory activities. It reduces the cytokine storm and prevent lung damage[127]. Cost-effectiveness, acceptable tolerance[128] and ease availability have made doxycycline, as a potential and rational option in patients with COVID-19. The pharmacokinetics of doxycycline in elderly, renal impairment, undernourished and hyperlipidaemic patients, patients with infection had already been studied. But data on the impact of sex, pregnancy, lactation or liver impairment on doxycycline pharmacokinetics is lacking[129]. Study demonstrated the varied response of doxycyclin with age. It was seen that above age of 65 years, serum concentrations of doxycyclin is more and volume of distribution is reduced, though definite reason behind this variation is unknown[130].

Conclusion

From the above discussion it is now quite clear that certain genes play a major role in the pathogenesis and severity of COVID-19 and also, how an individual's genetic makeup metabolizes and processes present COVID-19 therapies vis a vis therapeutic outcome. Further genetic studies need to be conducted for future application and recommendation of

pharmacogenomics in this pandemic. This type of individualisation of therapeutic strategies in COVID-19 shall further optimized the therapeutic outcome i.e. improves the safety and efficacy and decreases the adverse effects. As the feasibility and availability of rapid genetic testing (pre-emptive pharmacogenetic testing, point-of-care genetic testing) for proper and wider implementation of pharmacogenomics is a great challenge presently, in any situation the treatment of COVID-19 should be delayed or waited for genetic testing.

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References

[1] https://www.cebm.net/covid-19/global-covid-19-case-fatality-rates

[2] Yuki K, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology: A review. Clin Immunol. 2020 Jun; 215:108427. doi: 10.1016/j.clim.2020.108427. Epub 2020 Apr 20. PMID: 32325252; PMCID: PMC7169933.

[3] Bhaskar S, Sinha A, Banach M, Mittoo S, Weissert R, Kass JS, Rajagopal S, Pai AR and Kutty S (2020) Cytokine Storm in COVID-19 —Immunopathological Mechanisms, Clinical Considerations, and Therapeutic Approaches: The REPROGRAM Consortium Position Paper. Front. Immunol. 11:1648. doi: 10.3389/fimmu.2020.01648

[4] https://www.who.int/genomics/elsi/regulatory_data/region/euro/069/en

[5] https://twin-cities.umn.edu/news-events/research-brief-how-genetics-could-impact-covid-19-treatments

[6] Tanigawa Y, Rivas M. Initial review and analysis of COVID−19 host genetics and associated phenotypes. Preprints. 2020;2020030356. 10.20944/preprints202003.0356.v1

[7] Li W, Moore MJ, Vasilieva N, et al. Angiotensin−converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature. 2003;426(6965):450−454.

[8] Hoffmann M, Kleine−Weber H, Schroeder S, et al. SARS−CoV−2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020;181(2):271−280.e8.

[9] Hoffmann H, Geier M, Marzi A, et al. Susceptibility to SARS coronavirus S protein−driven infection correlates with expression of angiotensin converting enzyme 2 and infection can be blocked by soluble receptor. Biochem Biophys Res Comm. 2004;319:1216−1221.

[10] Cao Y, Li L, Feng Z, et al. Comparative genetic analysis of the novel coronavirus (2019−nCoV/SARS−CoV−2) receptor ACE2 in different populations. Cell discovery. 2020;6:11.

[11] Lippi G, Lavie CJ, Henry BM, Sanchis-Gomar F. Do genetic polymorphisms in angiotensin converting enzyme 2 (ACE2) gene play a role in coronavirus disease 2019 (COVID-19)? [published online ahead of print, 2020 Jun 29]. Clin Chem Lab Med. 2020;/j/cclm.ahead-of-print/cclm-2020-0727/cclm-2020-0727.xml. doi:10.1515/cclm-2020-0727

[12] Debnath M, Banerjee M, Berk M. Genetic gateways to COVID-19 infection: Implications for risk, severity, and outcomes. FASEB J. 2020 Jun 11:10.1096/fj.202001115R. doi: 10.1096/fj.202001115R. Epub ahead of print. PMID: 32525600; PMCID: PMC7300732.

[13] Gaddam RR, Chambers S, Bhatia M. ACE and ACE2 in inflammation: a tale of two enzymes. Inflamm Allergy Drug Targets. 2014;13:224−234.

[14] Thomas MC, Pickering RJ, Tsorotes D, et al. Genetic Ace2 deficiency accentuates vascular inflammation and atherosclerosis in the ApoE knockout mouse. Circ Res. 2010;107:888−897.

[15] Li M−Y, Li L, Zhang Y, Wang X−S. Expression of the SARS−CoV−2 cell receptor gene ACE2 in a wide variety of human tissues. Infect Dis Poverty. 2020;9:45.

[16] Blackwell JM, Jamieson SE, Burgner D. HLA and infectious diseases. Clin Microbiol Rev. 2009;22:370−385.

[17] Tian C, Hromatka BS, Kiefer AK, et al. Genome−wide association and HLA region fine−mapping studies identify susceptibility loci for multiple common infections. Nat Commun. 2017;8:599.

[18] Chen YM, Liang SY, Shih YP, et al. Epidemiological and genetic correlates of severe acute respiratory syndrome coronavirus infection in the hospital with the highest nosocomial infection rate in Taiwan in 2003. J Clin Microbiol. 2006;44:359−365.

[19] Lin M, Tseng HK, Trejaut JA, et al. Association of HLA class I with severe acute respiratory syndrome coronavirus infection. BMC Med Genet. 2003;4:9.

[20] Ng MH, Lau KM, Li L, et al. Association of human−leukocyte−antigen class I (B*0703) and class II (DRB1*0301) genotypes with susceptibility and resistance to the development of severe acute respiratory syndrome. J Infect Dis. 2004;190:515−518.

[21] Wang SF, Chen KH, Chen M, et al. 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. 2011;24:421−426.

[22] Keicho N, Itoyama S, Kashiwase K, et al. Association of human leukocyte antigen class II alleles with severe acute respiratory syndrome in the Vietnamese population. Hum Immunol. 2009;70:527−531.

[23] Campbell KM, Steiner G, Wells DK, Ribas A, Kalbasi A. Prediction of SARS−CoV−2 epitopes across 9360 HLA class I alleles. BioRxiv. 2020. 10.1101/2020.03.30.016931

[24] Middleton D, Williams F, Meenagh A, et al. Analysis of the distribution of HLA−A alleles in populations from five continents. Hum Immunol. 2000;61:1048−1052.

[25] Saxena A, Sharma G, Tyagi S, et al. HLA−A*02 repertoires in three defined population groups from North and Central India: Punjabi Khatries, Kashmiri Brahmins and Sahariya Tribe. Hla. 2019;93:16−23.

[26] Cao K, Moormann AM, Lyke KE, et al. Differentiation between African populations is evidenced by the diversity of alleles and haplotypes of HLA class I loci. Tissue Antigens. 2004;63:293−325.

[27] Lechien JR, Chiesa−Estomba CM, De Siati DR, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild−to−moderate forms of the coronavirus disease (COVID−19): a multicenter European study. Eur Arch Otorhinolaryngol. 20201–11.

[28] Klopfenstein T, Kadiane−Oussou NJ, Toko L, et al. Features of anosmia in COVID−19. Méd Mal Infect. 2020.

[29] Moein ST, Hashemian SMR, Mansourafshar B, Khorram−Tousi A, Tabarsi P, Doty RL. Smell dysfunction: a biomarker for COVID−19. Int Forum Allergy Rhinol. 2020.

[30] Secundo L, Snitz K, Weissler K, et al. Individual olfactory perception reveals meaningful nonolfactory genetic information. Proc Natl Acad Sci USA. 2015;112:8750−8755.

[31] Milinski M, Croy I, Hummel T, Boehm T. Major histocompatibility complex peptide ligands as olfactory cues in human body odour assessment. Proc Biol Sci. 2013;280:20122889.

[32] Younger RM, Amadou C, Bethel G, et al. Characterization of clustered MHC−linked olfactory receptor genes in human and mouse. Genome Res. 2001;11:519−530.

[33] Ehlers A, Beck S, Forbes SA, et al. MHC−linked olfactory receptor loci exhibit polymorphism and contribute to extended HLA/OR−haplotypes. Genome Res. 2000;10:1968−1978.

[34] Zhao M. Cytokine storm and immunomodulatory therapy in COVID− 19: Role of chloroquine and anti−IL−6 monoclonal antibodies. Int J Antimicrob Agents. 2020;105982.

[35] Zhang W, Zhao Y, Zhang F, et al. The use of anti−inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID−19): the perspectives of clinical immunologists from China. Clin Immunol. 2020;214:108393.

[36] Cox ED, Hoffmann SC, DiMercurio BS, et al. Cytokine polymorphic analyses indicate ethnic differences in the allelic distribution of interleukin−2 and interleukin−6. Transplantation. 2001;72:720−726.

[37] Hoffmann SC, Stanley EM, Cox ED, et al. Ethnicity greatly influences cytokine gene polymorphism distribution. Am J Transplant. 2002;2:560−567.

[38] Chong WP, Ip WK, Tso GH, et al. The interferon gamma gene polymorphism +874 A/T is associated with severe acute respiratory syndrome. BMC Infect Dis. 2006;6:82.

[39] Tang F, Liu W, Zhang F, et al. IL−12 RB1 genetic variants contribute to human susceptibility to severe acute respiratory syndrome infection among Chinese. PLoS One. 2008;3:e2183.

[40] Ulhaq, Zulvikar Syambani & Soraya, Gita. (2020). Anti-IL-6 Receptor Antibody Treatment for Severe COVID-19 and the Potential Implication of IL-6 Gene Polymorphisms in Novel Coronavirus Pneumonia. SSRN Electronic Journal. 10.2139/ssrn.3592878.

[41] Vuille-dit-Bille RN, Camargo SM, Emmenegger L, et al. Human intestine luminal ACE2 and amino acid transporter expression increased by ACE-inhibitors. Amino Acids 2015;47:693-705.

[42] Kuba K, Imai Y, Ohto-Nakanishi T, Penninger JM. Trilogy of ACE2: a peptidase in the renin-angiotensin system, a SARS receptor, and a partner for amino acid transporters. Pharmacol Ther 2010;128:119-128.

[43] Wein AN, McMaster SR, Takamura S, et al. CXCR6 regulates localization of tissue-resident memory CD8 T cells to the airways. J Exp Med 2019;216:2748-2762.

[44] Ellinghaus D, Degenhardt F, Bujanda L, Buti M, Albillos A, Invernizzi P, Fernández J, Prati D, Baselli G, Asselta R, Grimsrud MM, Milani C, Aziz F, Kässens J, May S, Wendorff M, Wienbrandt L, Uellendahl-Werth F, Zheng T, Yi X, de Pablo R, Chercoles AG, Palom A, Garcia-Fernandez AE, Rodriguez-Frias F, Zanella A, Bandera A, Protti A, Aghemo A, Lleo A, Biondi A, Caballero-Garralda A, Gori A, Tanck A, Carreras Nolla A, Latiano A, Fracanzani AL, Peschuck A, Julià A, Pesenti A, Voza A, Jiménez D, Mateos B, Nafria Jimenez B, Quereda C, Paccapelo C, Gassner C, Angelini C, Cea C, Solier A, Pestaña D, Muñiz-Diaz E, Sandoval E, Paraboschi EM, Navas E, García Sánchez F, Ceriotti F, Martinelli-Boneschi F, Peyvandi F, Blasi F, Téllez L, Blanco-Grau A, Hemmrich-Stanisak G, Grasselli G, Costantino G, Cardamone G, Foti G, Aneli S, Kurihara H, ElAbd H, My I, Galván-Femenia I, Martín J, Erdmann J, Ferrusquía-Acosta J, Garcia-Etxebarria K, Izquierdo-Sanchez L, Bettini LR, Sumoy L, Terranova L, Moreira L, Santoro L, Scudeller L, Mesonero F, Roade L, Rühlemann MC, Schaefer M, Carrabba M, Riveiro-Barciela M, Figuera Basso ME, Valsecchi MG, Hernandez-Tejero M, Acosta-Herrera M, D'Angiò M, Baldini M, Cazzaniga M, Schulzky M, Cecconi M, Wittig M, Ciccarelli M, Rodríguez-Gandía M, Bocciolone M, Miozzo M, Montano N, Braun N, Sacchi N, Martínez N, Özer O, Palmieri O, Faverio P, Preatoni P, Bonfanti P, Omodei P, Tentorio P, Castro P, Rodrigues PM, Blandino Ortiz A, de Cid R, Ferrer R, Gualtierotti R, Nieto R, Goerg S, Badalamenti S, Marsal S, Matullo G, Pelusi S, Juzenas S, Aliberti S, Monzani V, Moreno V, Wesse T, Lenz TL, Pumarola T, Rimoldi V, Bosari S, Albrecht W, Peter W, Romero-Gómez M, D'Amato M, Duga S, Banales JM, Hov JR, Folseraas T, Valenti L, Franke A, Karlsen TH; Severe Covid-19 GWAS Group. Genomewide Association Study of Severe Covid-19 with Respiratory Failure. N Engl J Med. 2020 Jun 17:NEJMoa2020283. doi: 10.1056/NEJMoa2020283. Epub ahead of print. PMID: 32558485; PMCID: PMC7315890.

[45] Cheng Y, Cheng G, Chui CH, et al. ABO blood group and susceptibility to severe acute respiratory syndrome. JAMA 2005;293:1450-1451.

[46] Zhao J, Yang Y, Huang H, et al. Relationship between the ABO blood group and the COVID-19 susceptibility. March 27, 2020. (https://www.medrxiv.org/content/10.1101/2020.03.11.20031096v2). preprint.

[47] Zietz M, Tatonetti NP. Testing the association between blood type and COVID-19 infection, intubation, and death. April 11, 2020. (https://www.medrxiv.org/content/10.1101/2020.04.08.20058073v1). preprint.

[48] Breiman A, Ruvën-Clouet N, Le Pendu J. Harnessing the natural anti-glycan immune response to limit the transmission of enveloped viruses such as SARS-CoV-2. PLoS Pathog 2020;16(5):e1008556-e1008556.

[49] Walls AC, Xiong X, Park Y-J, Tortorici MA, Snijder J, Quispe J, et al. Unexpected Receptor Functional Mimicry Elucidates Activation of Coronavirus Fusion. Cell. 2019;176:1026–39

[50] Comuzzie AG, Cole SA, Laston SL, et al. Novel genetic loci identified for the pathophysiology of childhood obesity in the Hispanic population. PLoS One 2012;7(12):e51954-e51954.

[51] Aziz M, Fatima R, Assaly R. Elevated interleukin-6 and severe COVID-19: A meta-analysis. J Med Virol 2020. April 28 (Epub ahead of print).

[52] Naitza S, Porcu E, Steri M, et al. A genome-wide association scan on the levels of markers of inflammation in Sardinians reveals associations that underpin its complex regulation. PLoS Genet 2012;8(1):e1002480-e1002480.

[53] Franchini M, Crestani S, Frattini F, Sissa C, Bonfanti C. ABO blood group and von Willebrand factor: biological implications. Clin Chem Lab Med 2014;52:1273-1276.

[54] Murray GP, Post SR, Post GR. ABO blood group is a determinant of von Willebrand factor protein levels in human pulmonary endothelial cells. J Clin Pathol 2020;73:347-349.

[55] Ozato K, Tsujimura H, Tamura T. Toll-like receptor signaling and regulation of cytokine gene expression in the immune system. BioTechniques. 2002;33:Suppl, 66–68, 70, 72 passim.

[56] Barreiro LB, Ben-Ali M, Quach H, et al. Evolutionary dynamics of human Toll-like receptors and their different contributions to host defense. PLoS Genet. 2009;5:e1000562

[57] Henmyr, V., Carlberg, D., Manderstedt, E., Lind-Halldén, C., Säll, T. et al. (2017) Genetic variation of the toll-like receptors in a Swedish allergic rhinitis case population. BMC Medical Genetics, 18(1): 18 https://doi.org/10.1186/s12881-017-0379-6.

[58] Totura AL, Whitmore A, Agnihothram S, et al. Toll-like receptor 3 signaling via TRIF contributes to a protective innate immune response to severe acute respiratory syndrome coronavirus infection. mBio. 2015;6:e00638-1615.

[59] Gralinski LE, Menachery VD, Morgan AP, et al. Allelic variation in the Toll-like receptor adaptor protein Ticam2 contributes to SARS-coronavirus pathogenesis in mice. G3 (Bethesda). 2017;7:1653-1663

[60] Stoermer KA, Morrison TE. Complement and viral pathogenesis. Virology. 2011;411:362-373.

[61] Noris M., Remuzzi G. Overview of complement activation and regulation. Semin Nephrol. 2013;33:479–492

[62] Fang C, Zhang X, Miwa T, Song WC. Complement promotes the development of inflammatory T-helper 17 cells through synergistic interaction with Toll-like receptor signaling and interleukin-6 production. Blood. 2009;114:1005-1015.

[63] Gralinski LE, Sheahan TP, Morrison TE, et al. Complement activation contributes to severe acute respiratory syndrome coronavirus pathogenesis. mBio. 2018;9(no.5,), e01753–18.

[64] Gao T, Hu M, Zhang X, et al. Highly pathogenic coronavirus N protein aggravates lung injury by MASP-2-mediated complement over-activation. MedRxiv. 2020. https://doi. org/10.1101/2020.03.29.20041962

[65] Goicoechea de Jorge E, López Lera A, Bayarri-Olmos R, Yebenes H, Lopez-Trascasa M, Rodríguez de Córdoba S. Common and rare genetic variants of complement components in human disease. Mol Immunol. 2018 Oct;102:42–57.

[66] Stoffman N, Magal N, Shohat T, et al. Higher than expected carrier rates for familial Mediterranean fever in various Jewish ethnic groups. European Journal of Human Genetics 2000;8 (4):307-10. 'doi:'10.1038/sj.ejhg .5200446

[67] Woo, Y., Kamarulzaman, A., Augustin, Y., Staines, H., Altice, F., & Krishna, S. (2020, April 12). A genetic predisposition for Cytokine Storm in life-threatening COVID-19 infection. https://doi.org/10.31219/osf.io/mxsvw

[68] Baykal Y, Saglam K, Yilmaz MI, et al. Serum's IL-2r, IL-6, IL-10 and TNF-α level in familial Mediterranean fever patients. Clinical Rheumatology 2003;22(2):99-101.doi: 10.1007/s10067-002-0682-1

[69] Manukyan G, Aminov R. Update on Pyrin Functions and Mechanisms of Familial Mediterranean Fever. Front Microbiol.2016-;7:456. Published 2016 Mar 31. doi:10.3389/fmicb.2016.00456

[70] Migitam K, Izumi Y, Jiuchi Y, et al. Familial Mediterranean fever is no longer a rare disease in Japan. Arthritis Research & Therapy 2016;18(1):175.doi:10.1186/s13075 016-1071-5

[71] Aldea A, Calafell F, Aróstegui JI, et al. The west side story: MEFV haplotype in Spanish FMF patients and controls, an evidence of high LD and a recombination "hot-spot" at the MEFV locus. Human Mutation 2004;23(4):399-99. doi: 10.1002/humu.9229

[72] Beheshtian M, Izadi N, Kriegshauser G, et al. Prevalence of common MEFV mutations and carrier frequencies in a large cohort of Iranian populations. Journal of Genetics 2016;95(3):667-74.doi:10.1007/s1 2041-016-0682-6

[73] Fujikawa K, Migita K, Tsukada T, Umeda M, Nonaka F, Kawakami A, et al. Interleukin 6 targeting therapy in familial Mediterranean fever. Clin Exp Rheumatol. 2013;31(3 Suppl 77):150–151.

[74] Umeda M, Aramaki T, Fujikawa K, Iwamoto N, Ichinose K, Terada K, et al. Tocilizumab is effective in a familial Mediterranea fever patient complicated with histologically proven recurrent fasciitis and myositis. IntJRheumDis. 2017;20(11):1868–1871.doi:10.1111/1756-185X.12776.

[75] Yilmaz S, Cinar M, Simsek I, Erdem H, Pay S. Tocilizumab in the treatment of patients with AA amyloidosis secondary to familial Mediterranean fever. Rheumatol Oxf Engl. 2015;54(3):564–565. doi:10.1093/ rheumatology / keu474.

[76] Nkhoma ET, Poole C, Vannappagari V, Hall SA, Beutler; The global prevalence of glucose-6-phosphate dehydrogenase deficiency: a systematic review and meta- analysis. Blood Cells Mol Dis. 2009;42(3):267. Epub 2009 Feb23.

[77] Al-Abdi S, Al Aamri M. G6PD deficiency in the COVID-19 pandemic: Ghost within Ghost. Hematol Oncol Stem Cell Ther. 2020 Apr 18. pii: S16583876(20)30044-3. doi:10.1016/j.hemonc.2020.04.002.

[78] Aydemir D, Ulusu NN. Is glucose- 6 phosphate dehydrogenase enzyme deficiency a factor in Coronavirus-19 (COVID-19) infections and deaths? Pathog Glob Health. 2020 May;114(3):109-110.doi:10.1080/20477724.2020.1751388.Epub2020Apr14.

[79] Wilmanski J, Villanueva E, Deitch EA, Spolarics Z. Glucose-6-phosphate dehydrogenase deficiency and the inflammatory response to endotoxin and polymicrobial sepsis. CritCare Med. 2007l35(2):510,518. doi: 10.1097/01.CCM.0000254337.50361.2E

[80] A. Savarino, J.R. Boelaert, A. Cassone, G. Majori, R. Cauda, Effects of chloroquine on viral infections: an old drug against today's diseases? Lancet Infect. Dis. 3 (11) (2003) 722–727

[81] Y. Yan, Z. Zou, Y. Sun, X. Li, K.F. Xu, Y. Wei, et al., Anti-malaria drug chloroquine is highly effective in treating avian influenza A H5N1 virus infection in an animal model, Cell Res. 23 (2) (2013) 300–302.

[82] E. Keyaerts, L. Vijgen, P. Maes, J. Neyts, M. Van Ranst, In vitro inhibition of severe acute respiratory syndrome coronavirus by chloroquine, Biochem. Biophys. Res. Commun. 323 (1) (2004) 264–268.

[83] M.J. Vincent, E. Bergeron, S. Benjannet, B.R. Erickson, P.E. Rollin, T.G. Ksiazek, et al., Chloroquine is a potent inhibitor of SARS coronavirus infection and spread, Virol. J. 2 (2005) 69.

[84] Horby P, Mafham M, Linsell L, Bell JL, Staplin N, Emberson JR, Wiselka M, Ustianowski A, Elmahi E, Prudon B, Whitehouse A. Effect of Hydroxychloroquine in Hospitalized Patients with COVID-19: Preliminary results from a multi-centre, randomized, controlled trial. MedRxiv. 2020 Jan 1.

[85]   https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments

[86] Chatterjee P, Anand T, Singh KJ, Rasaily R, Singh R, Das S, Singh H, Praharaj I, Gangakhedkar RR, Bhargava B, Panda S. Healthcare workers & SARS-CoV-2 infection in India: A case-control investigation in the time of COVID-19. Indian J Med Res. 2020 Jun 5.

[87] Choudhury S, Akam E, Mastana S. Genetic analysis of CYP2D6 polymorphism in Indian populations and its pharmacogenetic implications. Current Pharmacogenomics and Personalized Medicine (Formerly Current Pharmacogenomics). 2014 Jun 1;12(2):123-32.

[88] Differences in Genetic Polymorphisms of CYP2D6 in the U.S. Population: Clinical implications. Oncologist 2006; 11(2): 126-35.

[89] Serin A, Canan H, Alper B, Gulmen M. The frequencies of mutated alleles of CYP2D6 gene in a Turkish population. Forensic Sci Int 2012; 222(1-3): 332-4.

[90] Naveen AT, Adithan C, Soya SS, Gerard N, Krishnamoorthy R. CYP2D6 Genetic Polymorphism in South Indian Populations. Biol Pharm Bull 2006; 29(8): 1655-8.

[91] Grassmann, F. et al. Common synonymous variants in ABCA4 are protective for chloroquine induced maculopathy (toxic maculopathy). BMC Ophthalmol. 15, 18 (2015).

[92] Gautret, P. et al. Hydroxychloroquine and azithromycin as a treatment of COVID19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents 56, 105949. https://doi.org/10.1016/j.ijantimicag.2020.105949 (2020).

[93] Fohner, A. E., Sparreboom, A., Altman, R. B. & Klein, T. E. PharmGKB summary: macrolide antibiotic pathway, pharmacokinetics/pharmacodynamics. Pharmacogenetics Genomics 27, 164–167 (2017)

[94] He, X. J., Zhao, L. M., Qiu, F., Sun, Y. X. & Li-Ling, J. Influence of ABCB1 gene polymorphisms on the pharmacokinetics of azithromycin among healthy Chinese Han ethnic subjects. Pharm. Rep. 61, 843–850 (2009).

[95] FDA Letter to Gilead Sciences, Inc., https://www.fda.gov/media/137564/download (2020).

[96] Fact Sheet For Health Care Providers: Emergency Use Authorization (EUA) of Remdesivir (GS-5734™). https://www.fda.gov/media/137566/download (2020).

[97] Goldman, J. D. et al. Remdesivir for 5 or 10 days in patients with severe Covid-19. N. Engl. J. Med.,10.1056/NEJMoa2015301 (2020).

[98] https://theprint.in/health/dcgi-approves-use-of-favipiravir-for-restricted-emergency-use-in-moderate-covid-19cases/445163/#:~:text=New%20Delhi%3A%20India's%20drug%20regulator,continued%20its%20steady%20upward%20trend.

[99] Madelain V, et al. Ebola virus infection: review of the pharmacokinetic and pharmacodynamic properties of drugs considered for testing in human efficacy trials. Clin. Pharmacokinet. 2016;55:907–923.

[100] Hartmann, T., Terao, M., Garattini, E., Teutloff, C., Alfaro, J. F., Jones, J. P., & Leimkühler, S. (2012). The impact of single nucleotide polymorphisms on human aldehyde oxidase. Drug metabolism and disposition: the biological fate of chemicals, 40(5), 856–864. https://doi.org/10.1124/dmd.111.043828

[101] D'Avolio A, Cusato J, De Nicolò A, Allegra S, Di Perri G. Pharmacogenetics of ribavirin-induced anemia in HCV patients. Pharmacogenomics. 2016;17:925–941.

[102] Pineda-Tenor D, Garcia-Alvarez M, Jimenez-Sousa MA, Vazquez-Moron S, Resino S. Relationship between ITPA polymorphisms and hemolytic anemia in HCV-infected patients after ribavirin-based therapy: a meta-analysis. J. Transl. Med. 2015;13:320.

[103] Krishnan SM, Dixit NM. A formula to estimate the optimal dosage of ribavirin for the treatment of chronic hepatitis C: influence of ITPA polymorphisms. Antivir. Ther. 2012;17:1581–1592.

[104] Bhimrah, A. et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19 Infection. https://www.idsociety.org/COVID19guidelines (2020).

[105] Kowalec K, et al. Common variation near IRF6 is associated with IFN-beta-induced liver injury in multiple sclerosis. Nat. Genet. 2018;50:1081–1085.

[106] Link J, et al. Human leukocyte antigen genes and interferon beta preparations influence risk of developing neutralizing anti-drug antibodies in multiple sclerosis. PloS ONE. 2014;9:e90479.

[107] Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. https://www.covid19treatmentguidelines.nih.gov/ (2020).

[108] Lubomirov R, et al. ADME pharmacogenetics: investigation of the pharmacokinetics of the antiretroviral agent lopinavir coformulated with ritonavir. Pharmacogenet Genomics. 2010;20:217–230.

[109] Estrela RC, Santoro AB, Barroso PF, Tuyama M, Suarez-Kurtz G. CYP3A5 genotype has no impact on plasma trough concentrations of lopinavir and ritonavir in HIV-infected subjects. Clin Pharmacol Ther. 2008 Aug;84(2):205-7. doi: 10.1038/clpt.2008.12. Epub 2008 Feb 20. PMID: 18288082.

[110] Molto J, et al. Simultaneous pharmacogenetics-based population pharmacokinetic analysis of darunavir and ritonavir in HIV-infected patients. Clin. Pharmacokinet. 2013;52:543–553.

[111] Huang C, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395:497–506.

[112] Jimenez Morales A, et al. FCGR2A/FCGR3A gene polymorphisms and clinical variables as predictors of response to tocilizumab and rituximab in patients with rheumatoid arthritis. J. Clin. Pharm. 2019;59:517–531.

[113] Maldonado-Montoro M, Canadas-Garre M, Gonzalez-Utrilla A, Angel Calleja-Hernandez M. Influence of IL6R gene polymorphisms in the effectiveness to treatment with tocilizumab in rheumatoid arthritis. Pharmacogenomics J. 2018;18:167–172.

[114] Maldonado-Montoro M, Canadas-Garre M, Gonzalez-Utrilla A, Plaza-Plaza JC, Calleja-Hernandez MY. Genetic and clinical biomarkers of tocilizumab response in patients with rheumatoid arthritis. Pharm. Res. 2016;111:264–271.

[115] Damask, A & Boyapati, A & Hamilton, JD & Hamon, Sara & Paccard, Caroline & Parrino, J & Adelsberg, J & Graham, Neil & Penn, J & Lopez, A & Reid, J & Overton, J & Baras, A & Shuldiner, AR & Paulding, C. (2017). FRI0228 Ugt1a1 genetic variants are associated with increases in bilirubin levels in rheumatoid arthritis patients treated with sarilumab. Annals of the Rheumatic Diseases. 76. 570.2-571. 10.1136/annrheumdis-2017-eular.5016.

[116] Camp NJ, Cox A, di Giovine FS, McCabe D, Rich W, Duff GW. Evidence of a pharmacogenomic response to interleukin-l receptor antagonist in rheumatoid arthritis. Genes Immun. 2005;6:467–471. [PubMed] [Google Scholar]

[117] Jakafi (ruxolitinib) [package insert] https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/202192lbl.pdf (2011).

[118] Olumiant (baricitinib) [package insert] https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/207924s000lbl.pdf (2018).

[119] Yee SW, et al. Reduced renal clearance of cefotaxime in asians with a low-frequency polymorphism of OAT3 (SLC22A8) J. Pharm. Sci. 2013;102:3451–3457.

[120] Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. PLoS Med. 2006;3:e343.

[121] Song QQ, Xie WY, Tang YJ, Zhang J, Liu J. Genetic variation in the glucocorticoid pathway involved in interindividual differences in the glucocorticoid treatment. Pharmacogenomics. 2017;18:293–316.

[122] Benet LZ, Cummins CL, Wu CY: Unmasking the dynamic interplay between efflux transporters and metabolic enzymes. International journal of pharmaceutics. 2004, 277 (1-2): 3-9. 10.1016/j.ijpharm.2002.12.002.

[123] Hoffmeyer S, Burk O, von Richter O, Arnold HP, Brockmoller J, Johne A, Cascorbi I, Gerloff T, Roots I, Eichelbaum M, et al: Functional polymorphisms of the human multidrug-resistance gene: multiple sequence variations and correlation of one allele with P-glycoprotein expression and activity in vivo. Proc Natl Acad Sci USA. 2000, 97 (7): 3473-3478. 10.1073/pnas.050585397.

[124] Kudzi, W., Dodoo, A.N. & Mills, J.J. Genetic polymorphisms in MDR1, CYP3A4 and CYP3A5 genes in a Ghanaian population: a plausible explanation for altered metabolism of ivermectin in humans? BMC Med Genet 11, 111 (2010). https://doi.org/10.1186/1471-2350-11-111

[125] Dowling P. Pharmacogenetics: it's not just about ivermectin in collies. Can Vet J. 2006 Dec; 47(12):1165-8. PMID: 17217086; PMCID: PMC1636591.

[126] Zhao X, Ogunwobi OO, Liu C (2011) Survivin Inhibition Is Critical for Bcl-2 Inhibitor-Induced Apoptosis in Hepatocellular Carcinoma Cells. PLoS ONE 6(8): e21980. doi:10.1371/journal.pone.0021980

[127] Malek AE, Granwehr BP, Kontoyiannis DP. Doxycycline as a potential partner of COVID-19 therapies. ID Cases. 2020; 21:e00864. Published 2020 Jun 6. doi:10.1016/j.idcr.2020.e00864

[128] Conforti C, Giuffrida R, Zalaudek I, Di Meo N. Doxycycline, a widely used antibiotic in dermatology with a possible anti-inflammatory action against IL-6 in COVID-19 outbreak [published online ahead of print, 2020 Apr 20]. Dermatol Ther. 2020; e13437.

[129] Saivin S, Houin G. Clinical pharmacokinetics of doxycycline and minocycline. Clin Pharmacokinet 1988; 15: 355–66

[130] Bocker R, Muhlberg W, Platt D et al. Serum level, half-life and apparent volume of distribution of doxycycline in geriatric patients. Eur J Clin Pharmacol 1986; 30: 105–8.