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# Pharmacogenetics- gene and SARS-COVID 19 Medication

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## Presenter Information

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# Pharmacogenetics- gene and SARS-COVID 19 Medication

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**Abstract.** An analysis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) genomes collected from the patients worldwide has identified mutations in the virus that could aid in drug and vaccine development. The researchers found that the virus's genetic diversity in most countries is similar to what it is globally, suggesting that it was introduced repeatedly by many infected people in each country rather than by a "patient zero." The genetic analysis found 198 mutations that have occurred more than once. "Mutations in themselves are not a bad thing it is nothing to suggest SARS-CoV-2 is mutating faster or slower than expected. Several factors, including pharmacogenetics, it is possible to contribute to inter-individual variability in drug response. However, till today little is known about the host genetics interaction with infection and COVID-19 progression. To understand the role of host gene, we review the current literature, aggregate readily available genetic resources, and provide some updated analysis relevant to COVID-19 and associated phenotypes.

**Keywords**: SARS-CoV-2, gene information, genetic variability, gene expression, gene polymorphism

## 1 Introduction

Inter-individual variability in drug disposition is major cause for lack of efficacy or adverse reactions to pharmacological treatment in up to 50% of all patients, posing big challenges for medical care and drug development. Post-market safety events resulting in drug withdrawals, boxed warnings or safety communications affect 32% of all novel therapeutics approved by FDA from 2001 to 2010, leading to substantial economic losses for pharmaceutical industry [1].

Furthermore, epidemiological data from the US shows that adverse drug reactions (ADRs) cause 8.25% and 19.2% increase of hospital stay length and death rate, respectively, and severe ADRs are estimated to be the 4th-6th leading cause of death [2]. It is estimated that 20–30% of these negative effects can be attributed to genetic variations and more than 200 pharmacogenomic biomarkers have by now been incorporated into pharmacogenetics labels that can provide clinically actionable information regarding drug choice or dosing.

The absorption, distribution, metabolism, elimination (ADME) of most drugs are complex and involve multiple enzymes and transporter systems. As a consequence, it is likely that the effects of functional alteration in one ADME protein on drug response phenotypes can be amplified or compensated if they coincide with functional variation in another component involved in the disposition of the same drug [3].

Importantly, while such combinatorial pharmacogenetic effects are plausible, only few examples have been presented to date, including additive effects of functional CYP2D6 duplications and UGT2B7*2 genotype for codeine toxicity in breastfed neonates [4] and the balance between active CYP2D6 and CYP2C19 alleles for amitryptiline toxicity [5].

Transmission [6] of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) occurs primarily via respiratory droplets from face-to-face contact and, to a lesser degree, via contaminated surfaces. Aerosol spread may occur, but the role of aerosol spread in humans remains unclear. An estimated 48%to 62%of transmission may occur via presymptomatic carriers.

Common symptoms [7] in hospitalized patients include fever (70%-90%), dry cough (60%-86%), shortness of breath (53%- 80%), fatigue (38%), myalgias (15%-44%), nausea/vomiting or diarrhea (15%-39%), headache, weakness (25%), and rhinorrhea (7%). Anosmia or ageusia may be the sole presenting symptom in approximately 3%of individuals with COVID-19.

Common laboratory abnormalities [8] among hospitalized patients include lymphopenia (83%), elevated inflammatory markers (eg, erythrocyte sedimentation rate, C-reactive protein, ferritin, tumor necrosis factor-α, IL-1, IL-6), and abnormal coagulation parameters (e.g, prolonged prothrombin time, thrombocytopenia, elevated D-dimer [46%of patients], low fibrinogen).

Common complications [7, 9, 10, 11, 12, 13] among hospitalized patients with COVID-19 include pneumonia (75%); acute respiratory distress syndrome (15%); acute liver injury, characterized by elevations in aspartate transaminase, alanine transaminase, and bilirubin (19%); cardiac injury, including troponin elevation (7%-17%), acute heart failure, dysrhythmias, andmyocarditis; prothrombotic coagulopathy resulting in venous and arterial thromboembolic events (10%-25%); acute kidney injury (9%); neurologic manifestations, including impaired consciousness (8%) and acute cerebrovascular disease (3%); and shock (6%).

## 1.1 Drug and gene information

162 drugs with pharmacogenetic labels were obtained from FDA [14], CPIC [15] and DPWG [16]. This list was complemented with 100 top selling drugs, resulting in a total of 212 drugs for analysis. ADME fingerprints of all compounds were extracted from DrugBank.

### 1.2 Pharmacogenetic data

Genetic variability data was obtained from Ingelman-Sundberg et al., 2018[17]. The minor allele frequencies (MAFs) of variations classified as functional were aggregated and complemented with the functional variants CYP1A2*1C (rs2069514), CYP1A2*1F (rs762551), CYP2C19*17 (rs12248560), CYP3A4*22 (rs35599367), CYP3A5*3 (rs776746), CYP2B6*22 (rs34223104), CYP2C8*3 (rs10509681, rs11572080), CYP2C9*3 (rs1057910), CYP2E1*2 (rs72559710) and UGT1A1*28 (rs8175347), which were not included in the analyses. Furthermore, rs11572078 in CYP2C8 and rs2297595 in DPYD were removed as false-positive predictions.

Zhou and Volker 2020 [18] extracted ADME information from 212 drugs encompassing 94 associated genes involved in drug disposition or toxicity. The selected drugs were distributed across therapeutic areas with most compounds being used in psychiatry (n = 40), oncology (n = 35) and cardiology (n = 28; Fig. 1). The genes that were implicated in the disposition of most drugs were CYP3A4 (n = 141 drugs), ABCB1 (n = 94 drugs), CYP2D6 (n = 92 drugs) and CYP2C19 (n = 64 drugs).

In addition to gene family- or subfamily-wide interactions, Zhou, Volker 2020 [18] found highly specific interactions between individual gene pairs. For instance, of 94 ABCB1 substrates in our data set, 81 were also substrates of CYP3A4 (Fig. 2A). Accordingly, drugs that were transported by ABCB1 were 19.7% more likely to be also CYP3A4 substrates than expected by chance. Similarly, implication of CYP2D6 was a decent predictor of CYP1A2 and CYP3A4 metabolism with ΔP values of 0.14 and 0.13, respectively (Fig. 2B). Notably however, DPCYP3A4, CYP2D6 substantially lower than ΔPCYP3A4, ABCB1. Further notable associations were found for SLCO1B1 that shared substantial overlap with ABCC2 (ΔP = 0.57) and ABCB1 (ΔP = 0.43; Fig. 2C).

Finally, TPMT overlapped with NUDT15 (ΔP = 0.74), ABCC5 (ΔP = 0.72) and SLC29A1 (ΔP = 0.72) but not with CYPs (ΔP < 0), UGTs (ΔP < 0) or SULTs (ΔP < 0; Fig. 3D) [18].

### 1.3 Gene expression of *ACE2* and *TMPRSS2* variants

Asselta et al., 2020 [22] found no significant evidence for *ACE2;* it is not sure if *ACE2* is associated with disease severity/sex bias in the Italian population, *TMPRSS2* levels and genetic variants proved to be possible candidate disease modulators, contributing to the observed epidemiological data among Italian patients.

Children account for less than 2% of identified cases of coronavirus disease 2019 (COVID-19) [20, 23]. It is hypothesized that the lower risk among children is due to differential expression of angiotensin-converting enzyme 2 (ACE2) [21], the receptor that severe acute respiratory syndrome coronavirus 2 (SARSCoV- 2) uses for host

entry. Dong et al., [21] investigated *ACE2* gene expression in the nasal epithelium of children and adults.

The results from this study show age-dependent expression of *ACE2* in nasal epithelium, the first point of contact for SARS-CoV-2 and the human body. Covariate-adjusted models showed that the positive association between *ACE2* gene expression and age was independent of sex and asthma. Lower *ACE2* expression in children relative to adults may help explain why COVID-19 is less prevalent in children [21]. A limitation of this study is that the sample did not include individuals older than 60 years.

The analysis by Asselta et al., 2020 [22] suggests a role for *TMPRSS2* variants and expression levels in modulating COVID-19 severity, a hypothesis that fosters a rapid experimental validation on large cohorts of patients with different clinical manifestations.

### 1.4 Functional of CYP2D6 by assessing primaquine 5-hydroxylation

Cytochrome P450 (CYP) 2D6 is involved in the metabolism of approximately 25% of clinically used drugs, including antidepressants, β-blockers, anticancer drugs, opioid analgesics, and antimalarial drugs [23].

Multiplexed targeted genotyping and MLPA analysis of 427 African–American, Asian, Caucasian, Hispanic and Ashkenazi Jewish individuals identified the frequencies of 16 variant *CYP2D6* alleles and the copy number of exons 1, 4, 6 and 3 downstream region. It is shown that CYP2D6 metabolized Hydroxychloroquine [24].

### 1.5 Function and polymorphism of CYP3A4 and CYP3A5

Among the four cytochrome P450 (CYP) 3A genes, the most expressed in the liver are CYP3A4 and CYP3A5. Till today are reported eighty single nucleotide polymorphysms (SNP) of CYP3A4/5 to the Human P450 Allele Nomeclature Committee. CYP3A4 alleles with minimal function compared with wild type include the CYP3A4*6 and CYP4*17. The alleles which have moderately decreased or altered activity include: CYP3A4*2,*8,*11,*12,*13,*16, and *18. CYP3A5 alleles with minimal function include the splice variants CYP3A5*3,*5,*6 and CYP3A5*10, as well as the null allele CYP3A5*7. Alleles with moderately decreased catalytic activity include CYP3A5*8 and CYP3A5*9. This report reviews the current progress in the functional characterization of CYP3A4 and CYP3A5 SNPs and provides genotyping tests for possible defective variants. A combination of genotyping tests for defective CYP3A4/CYP3A5 haplotypes will be necessary to understand the variations in the metabolism and clinical toxicity of a wide variety of clinical drugs, since these two CYP proteins have overlapping substrate specificities [25].

### 1.6 Toll like receptor 7 (TLR7)

van der Made [26] and colleagues 2020 describe 2 independent families with rare germline variants in an innate immune-sensing gene, toll-like receptor 7 (*TLR7*), that lead to severe disease in males who inherit the mutated gene on a single copy of their X chromosome. The study implicates TLR7 as a critical node in recognizing SARS-

CoV-2 and initiating an early immune response to clear the virus and prevent the development of COVID-19.

The study by van der Made and colleagues 2020 implicates insufficient control of viral replication via TLR7 and innate immune sensing as a driver of severe COVID-19 in young, previously healthy males from 2 independent families. In the first family, the index case was a male patient, age 32 years, with severe COVID-19 requiring mechanical ventilation in the intensive care unit (ICU). His 29-year-old brother died of COVID-19. Whole-exome sequencing was performed in the index case, leading to the discovery of a 4-nucleotide hemizygous deletion likely leading to a predicted total loss of function of *TLR7* by introducing a premature termination codon (c.2129_2132del; p.[Gln710Argfs*18]).

The index case in the second family was a male patient, age 21 years, with severe COVID-19 complicated by pulmonary embolisms requiring mechanical ventilation in the ICU. His 23-year-old brother had severe COVID-19 and required ICU care. Exome sequencing revealed a missense variant (c.2383G>T; p.[Val795Phe]), which was predicted as deleterious in all in silico prediction tools.

In conclusion, the study by van der Made [26] and colleagues 2020 provides evidence that rare mutations in *TLR7* were associated with severe COVID-19 in young males from 2 independent families. While rare mutations in *TLR7* are unlikely to be a major driver of severe disease in most individuals infected with SARS-CoV-2, the genetic study begins to unravel the molecular underpinnings of COVID-19. As additional genetic loci are identified, such data could lead to improved diagnostics and therapeutics, including rational repurposing of existing anti-inflammatory therapies in either early infection or late stage severe disease.

In the study by Caspar et al [27] a series of 4 young male patients with severe COVID-19, rare putative loss-of-function variants of X-chromosomal *TLR7* were identified that were associated with impaired type I and II IFN responses. These preliminary findings provide insights into the pathogenesis of COVID-19.

### 1.7 UGT1A1 gene UDP (glucuronosyltransferase family 1 member A1)

The *UGT1A1* gene belongs to a family of genes that provide instructions for making enzymes called UDP-glucuronosyltransferases. These enzymes perform a chemical reaction called glucuronidation, in which a compound called glucuronic acid is attached (conjugated) to one of a number of different substances.

The protein produced from the *UGT1A1* gene, called the bilirubin uridine diphosphateglucuronosyl transferase (bilirubin-UGT) enzyme; *UGT1A1* is the only enzyme that glucuronidates bilirubin, a substance produced when red blood cells are broken down. *UGT1A1* converts the toxic form of bilirubin (unconjugated bilirubin) to its nontoxic form (conjugated bilirubin).

Chinese research group Yao et al., 2020 [28] has made research by, biochemical indicators of liver, blood clotting mechanism, routine blood test, UGT1A1 * 28 gene polymorphism and other data of 40 cases with COVID-19 admitted to the isolation ward of Tangdu Hospital were retrospectively analyzed. They came to conclusion that COVID-19 combined with liver function injury may be due to the slight elevation of transaminase, mostly around the second week of the disease course. Severe patients

have a higher proportion of liver injury, and critical type is an independent risk factor for liver injury.

### 1.8 VDR gene vitamin D receptor

The *VDR* gene is responsible for making a protein called vitamin D receptor (VDR), which allows the body to respond to vitamin D. This vitamin can be acquired from foods in the diet or made in the body with help from sunlight exposure. Vitamin D is involved in maintaining the proper balance of several minerals in the body, such as calcium and phosphate; both calcium and phosphate are essential for the normal formation of bones and teeth. One of vitamin D's major roles is to control the absorption of calcium and phosphate from the intestines into the bloodstream. Vitamin D is also involved in several processes unrelated to bone and tooth formation.

The VDR protein attaches (binds) to the active form of vitamin D, known as calcitriol. This interaction allows VDR to partner with another protein called retinoid X receptor (RXR).

Vitamin D is produced in the skin under the influence of UVB-light from the sun or obtained via the diet by eating fatty fish, enriched dairy products or supplements. Vitamin D is known to support a healthy bone and severe deficiency may lead to osteomalacia or the rickets, which still occur in poor areas of the world. In addition, vitamin D support key functions in many organs, including the brain, muscle and the immune systems [29]. In fact, the vitamin D receptor (VDR) is expressed in most cell types and may activate somewhere between 200-500 genes, many related to the immune system [30].

Substantial evidence supports a link between vitamin D deficiency and COVID-19 severity but it is all indirect. Community-based placebo-controlled trials of vitamin D supplementation may be difficult. Further evidence could come from study of COVID-19 outcomes in large cohorts with information on prescribing data for vitamin D supplementation or assay of serum unbound 25(OH) vitamin D levels. Meanwhile vitamin D supplementation should be strongly advised for people likely to be deficient [31].

Finally, the field of vitamin D and Covid-19 is very active and several trials are under way. Thus, new data will come, which may change these conclusions. However, in the meantime the conclusions above can be followed and we have massive data to say that vitamin D at low doses (1000-2000 IU/day) are safe and not harmful, which is in line with the historical proverb: primum non nocere (first, do no harm) – but potentially we may prevent a number of ARIs and perhaps also Covid-19 [30].

### 1.9 APOE e4 Gene

The *ApoE* e4 genotype is associated with both dementia and delirium [32], with the e4e4 (homozygous) genotype associated with a 14-fold increase in risk of

Alzheimer's disease [33] compared to the common e3e3 genotype, in populations with European ancestries. Kuo et al 2020 [32], therefore, aimed to test associations between *ApoE* e4 alleles and COVID-19 severity, using the UKB data.

The *ApoE* e4e4 allele increases risks of severe COVID-19 infection, independent of preexisting dementia, cardiovascular disease, and type-2 diabetes. *ApoE* e4 not only affects lipoprotein function (and subsequent cardio-metabolic diseases) but also moderates macrophage pro-/anti-inflammatory phenotypes [34]. The novel coronavirus SARS-CoV-2 causing COVID-19 uses the ACE2 receptor for cell entry. ACE2 is highly expressed in type II alveolar cells in the lungs, where *ApoE* is one of the highly co-expressed genes [35]. Further investigation is needed to understand the biological mechanisms linking *ApoE* genotypes to COVID-19 severity.

## 2. Discussion

We present a review and analysis of COVID-19 host genetics and related phenotypes. At the beginning of the current outbreak of COVID-19 in January 2020, the guidelines are adopted for treating patients infected with SARS-CoV-2 were established based on the previous experience with the MERS outbreak, although clinical outcomes still need to be evaluated [43, 44]. We hope that this paper will help clinicians understand, prioritize and monitor the drugs being used until results of clinical trials are available.

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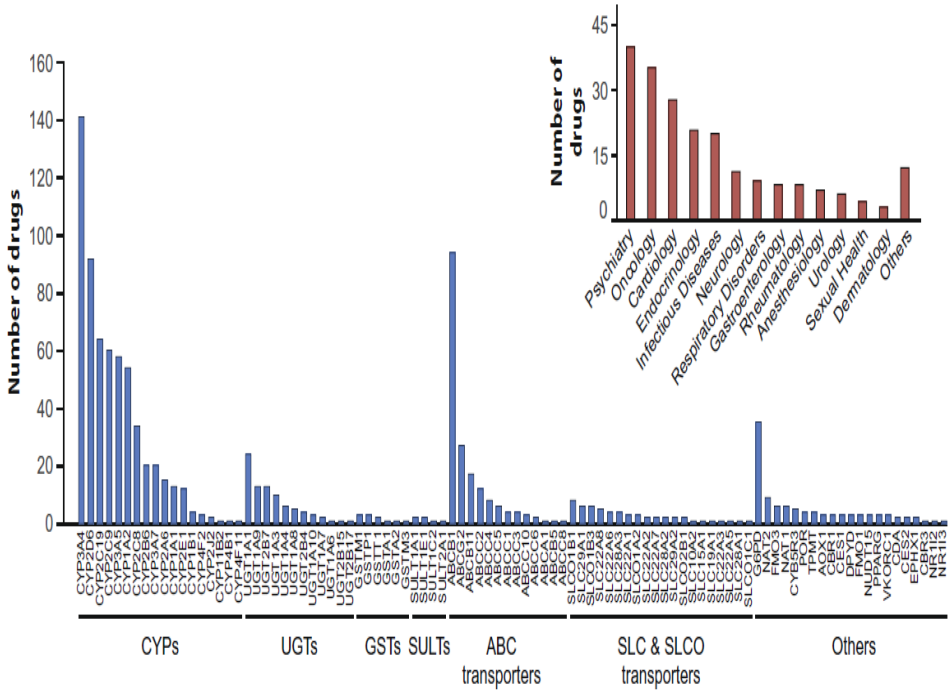

**Fig. 1**. Overview of the genes and drug considered for analysis. Large column plot depicts the number of drug associations per gene. In total n = 212 genes were considered. The inlet shows the distribution of drugs across therapeutic areas.

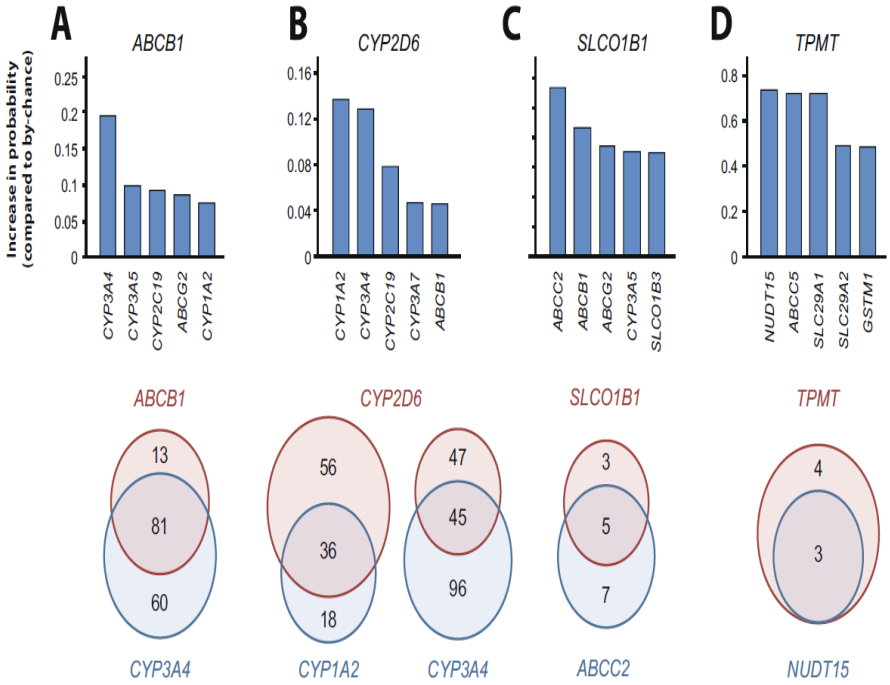


**Fig. 2**. Examples of specific interactions between pharmacogenes. The difference (DP) between the posterior probability that gene 2 is involved in the disposition of a drug under the condition that gene 1 is involved compared to the unconditional probability for metabolism by gene 1, defined as $\Delta P = P(gene2|gene1) \_ P(gene2)$ is shown for gene1 as ABCB1 (A), CYP2D6 (B), SLCO1B1 (C) and TPMT (D) and the respective most closely correlated genes. Venn diagrams show the overlap of the number of drugs for the top hits for each respective gene.