Letter to editor

Drug repurposing against COVID-19 by GWAS

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ABSTRACT

This note is prepared by the authors of a recent publication on shared genetic architecture of drug response based on summary statistics from genome-wide association studies (GWAS) to propose a drug repurposing approach for the treatment of coronavirus COVID-19. The authors proposed that *in silico* studies may be preceded by analyzing shared genetic architecture of drug response based on existing GWAS.

***Keywords*:** COVID-19, genome-wide association studies, drug responsing, *in silico*

Since the development of drugs has been increasingly challenging due to newly identified mechanisms of action, drug repurposing has become an attractive option for the rapid identification of potential therapeutics for combating COVID-19 pandemic. For this purpose data generated through Genome-Wide Association Studies (GWAS) hold great potential for identifying novel loci for response to drug without priori hypothesis [1-4]. Animal and cell-based models seldom mimic the human physical state for translating preclinical outcomes into clinical practice. As GWAS are based on clinical human samples with actual manifestation of effect, the findings are more

realistically reflect genetic basis of response to drugs [2,5,6].

In the last two decades, an increasing number of GWAS methods and tools have been available for exploring the impact of Single Nucleotide Polymorphism (SNP) on individual drug response, for investigating targets and effects of drugs, and prioritize the causal genes involved [7-8]. Although small effect size of individual SNPs on susceptibility of diseases/traits has been a matter of serious concern throughout the GWAS era, this modest effect size does not necessarily dictate low efficacy of therapeutic potential of the corresponding targets [1,9,11]. Therefore, GWAS data can prove a potential source for drug discovery and repositioning.

Recent studies have demonstrated that genetically supported targets involving causal genes are more likely to be successful in Phases II and III of the drug development process [12,13]. Once identified, the target gene for the associated SNPs need to be prioritized as the associated SNP may not necessarily represent functionally most relevant gene. Along with the prioritization, it is often desirable to underscore directionality of SNPS-gene relationship in order to determine drug repositioning. For instance, the identified SNPS may be related to the upregulation of to the target gene and its protein product inhibitor may be a potential repositioning candidate [2].

Besides prioritizing the corresponding target gene for the associated SNP, it is preferable to also determine the directionality of such relationships to facilitate drug repositioning. For example, if the identified SNP causes an upregulation of gene X leading to increased risk of a disease, then an inhibitor of its protein product may be considered a repositioning candidate [2,14].

The World Health Organization (WHO) announced to help launch four mega trials against COVID-19. The WHO-backed trials are focusing on drugs that are thought to directly block SARS-CoV-2 – the virus strain that causes coronavirus COVID-19: Remdesivir, lopinavir/ritonavir, chloroquine and hydroxychloroquine [3]. There are countless other small scale trials coordinated in countries worldwide, trials involving passive immunization and blocking some components of immune system [3,15].

Clustering of GWAS data have been used to discover phenotypic patterns of cells/tissues, sensitivity to drugs, and to detect artifacts of experimental conditions [16-18]. Exploring a meaningful pattern of genome-wide correlations would require identification of SNP subsets shaping genetic architecture

differentially and giving insight into the etiological mechanism underlying the phenotype (disease, response to a drug) that cannot be detected by standard GWAS [19]. We recently introduced a method for analysis of shared genetic architecture of drug response based on GWAS summary statistics and reported six groups of the 40 drugs sharing 211 SNP. The phenotypic pattern of drugs, associated SNPs and related genes in our study revealed a possibility for understanding etiological interactions and therapeutic mechanism of actions for different drugs by highlighting relevant biological pathways [1]. One of the clusters in our study, comprised efavirenz and rifampicin, an antiviral and an anti-tubercular drug, respectively. There could be other combinations that might be suggested for clinical trials and perhaps would show beneficial values in controlling the recent viral pandemic outbreak.

A recent *in silico* study has identified rifampicin as the best hit among the selected drugs against COVID-19 [3]. Rifampicin is a well-established medicine for the treatment of tuberculosis and has a stronger binding affinity for COVID-19 Main Protease (MPro) in comparison to the other drug compounds taken in the studies [3,20]. Therefore, use of rifampicin has been suggested as a repurposed drug for the treatment of COVID-19.

An earlier study showed that atazanavir, an antiretroviral medication used to treat and prevent the human immunodeficiency virus (HIV), is the best chemical compound, showing a inhibitory potency with Kd of 94.9 nM against the 2019-nCoV 3C-like proteinase, followed by efavirenz (199.2 nM), ritonavir (204.0 nM), and dolutegravir (336.9 nM). Therefore, clustering of efavirenz and rifampicin in our study [1], suggests use of efavirenz (the brand names Sustiva) for the treatment of COVID-19. However, this warrants further *in silico* studies of all other potential drugs for COVID-19 before initiating *in vitro* and clinical trials [3,21-30]. We propose that all such *in silico* studies may be preceded by analyzing shared genetic architecture of drug response based on existing GWAS, data using the method described by us earlier [1].

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