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Drug-disease interactions of differentially expressed genes in COVID-19 liver samples: an *in-silico* analysis

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Key words: COVID-19; liver; cytochrome P450; gene expression.

Abstract. While COVID-19 liver injuries have been reported in various studies, concerns are raised about disease-drug reactions in COVID-19 patients. In this study, we examined the hypothesis of gene-disease interactions in an in-silico model of gene expression to seek changes in cytochrome P450 genes. The Gene Expression Omnibus dataset of the liver autopsy in deceased COVID-19 patients (GSE150316) was used in this study. Non-alcoholic fatty liver biopsies were used as the control (GSE167523). Besides, gene expression analysis was performed using the DESeq/EdgeR method. The GO databases were used, and the paths were set at $p<0.05$. The drug-gene interaction database (DGIdb) was searched for interactions. According to the results, 5,147 genes were downregulated, and 5,122 genes were upregulated in SARS-CoV-2 compared to healthy livers. Compared to the cytochromes, 34 cytochromes were downregulated, while 4 cytochromes were upregulated among the detected differentially expressed genes (DEG). The drug-gene interaction database (DGIdb) provided a list of medications with potential interactions with COVID-19 as well as metacetamol, phenethyl isocyanate, amodiaquine, spironolactone, amiloride, acenocoumarol, clopidogrel,

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phenprocoumon, trimipramine, phenazepam, etc. Besides, dietary compounds of isoflavones, valerian, and coumarin, as well as caffeine metabolism were shown to have possible interactions with COVID-19 disease. Our study showed that expression levels of cytochrome P450 genes could get altered following COVID-19. In addition, a drug-disease interaction list is recommended to be used for evaluations in clinical considerations in further studies.

Interacciones fármaco –enfermedad de genes diferencialmente expresados en muestras de hígado de COVID-19: un análisis *in-silico*.

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Palabras clave: COVID-19; hígado; citocromo P450; expresión génica.

Resumen. Mientras que se han informado sobre lesiones hepáticas por COVID-19 en diversos estudios, las preocupaciones se elevan acerca de las reacciones enfermedad-fármaco en los pacientes con COVID-19. En este estudio, investigamos la hipótesis de las interacciones gen-enfermedad en un modelo *in-silico* de la expresión génica para buscar los cambios en los genes del citocromo P450. En este estudio se utilizó el conjunto de datos Ómnibus de la Expresión Génica de la autopsia hepática en los pacientes fallecidos por COVID-19 (GSE150316). Las biopsias de hígado graso no alcohólico se utilizaron como controles (GSE167523). Además, el análisis de la expresión génica se realizó mediante el método DESeq / EdgeR. Se utilizaron las bases de datos GO y las rutas fueron ajustadas en $p < 0,05$. La base de datos de la interacción fármaco-gen (DGIdb) fue investigada para las interacciones. Según los resultados, 5.147 genes se regularon a la baja y 5.122 genes se regularon al alza en el SARS-CoV-2 en comparación con los hígados sanos. En comparación con los citocromos, 34 citocromos se regularon a la baja, mientras que 4 citocromos fueron regulados al alza entre la expresión de los genes detectados diferencialmente (DEG). La base de datos de la interacción fármaco-gen (DGIdb) proporcionó una lista de medicamentos con las interacciones potenciales con COVID-19, así como con metacetamol, fenetilo isocianato, amodiaquina, espironolactona, amilorida, acenocumarol, clopidogrel, fenprocoumon, trimipramina, fenazepam, etc. También, los compuestos dietéticos de isoflavonas, valeriana y cumarina, así como el metabolismo de la cafeína han mostrado tener posibles interacciones con la enfermedad COVID-19. Nuestro estudio demostró que los niveles de la expresión de los genes del citocromo P450 podrían quedar alterados siguiendo COVID-19. Además, se recomienda utilizar una lista de fármaco-enfermedad interacción para evaluar en las consideraciones clínicas en otros estudios adicionales.

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INTRODUCTION

COVID-19 manifestations in the liver have been recently reported. According to available evidence, 2-11% of COVID-19 patients develop liver disease. In 14-53% of the cases, abnormal levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) have been seen during progression of the disease (1). In mild cases of COVID-19, liver damage is often transient and can return to its normal state without any special treatment. However, patients with severe COVID-19 disease appear to have more severe liver function disorders (2). Liver damage in patients with SARS-CoV-2 infection could be directly due to viral infection of liver cells (3) and immune-mediated inflammations, such as cytokine storm. In addition, liver damage could be due to toxicity of prescribed medications for COVID-19 (4). In patients with critical forms of COVID-19, it may lead to liver failure (5, 6). Many concerns have been raised about the possibility of significant disease-drug interactions in COVID-19 patients through modulations of Cytochrome P450s, as Ghiaty *et al.* reported (7). Human cytochrome P450 enzymes are monooxygenases playing a decisive role in the synthesis of cholesterol, steroids, and other lipids, as well as in detoxification and metabolism of drugs and environmental chemicals. Any changes in expression of the cytochrome P450 gene or its post-transcriptional level might dysregulate its function (8). The cytochrome P450 enzyme is responsible for metabolizing a wide range of internal and external organic compounds. Besides, many drug compounds involved in treatment are substrates for this enzyme. This study aims to examine the hypothesis of gene-disease interactions in an *in-silico* model of gene expressions to seek changes in cytochrome P450 genes.

MATERIALS AND METHODS

We conducted a meta-analysis of Gene Expression Omnibus (GEO) data on the livers of COVID-19 patients. Datasets of COVID-19 patients were searched using the keywords of "COVID-19", "SARS-CoV-2", and "new Coronavirus" through a GEO search. The GEO databases were chosen from 25 available sources based on the inclusion criterion that was available gene expression data of the livers of COVID-19 individuals. Based on the similarities to the COVID-19 datasets chosen, control datasets were quarried. Accordingly, raw read counts (Illumina platforms) of liver autopsy in deceased COVID-19 patients of the GSE150316 GEO dataset were included with three samples in this study. Besides, GSE167523 samples of humans' non-alcoholic fatty liver disease were used as controls.

Gene expression analysis was performed using the DESeq/EdgeR method, via iDEPR-Shiny software (9). Lowly expressed genes were excluded from the dataset through data processing. Next, gene IDs were converted to a similar format and data were log transformed for PCA analysis. Besides, differentially expressed genes (DEGs) were detected using the DESeq2 package with the false detection threshold of (FDR) < 0.1 and a change equal and higher than 2.

To identify important biological pathways based on common genes affected in the two datasets, GO databases were used, with the paths of $p < 0.05$, according to hypergeometric analysis, having been reported as affected paths. To identify biological pathways involved in the studied disease, the drug-gene interaction database (DGIdb) and GO were used. To interpret the list of the genes based on GO databases, hypergeometric statistic tests were used to read the GO pathways and to build a gene expression regulation network.

RESULTS

Processing

A total of 26,364 genes were evaluated in 10 samples with the settings of the counts per million reads mapped (CPM) = 0.5. The difference between replicates in the SARS-CoV-2 samples compared to healthy livers showed a significant alteration to the expression of hundreds of genes in SARS-CoV-2 infected livers versus the control samples based on the analysis of the principal components (PCA) that explained for 67% of the variance difference between SARS-CoV-2 and control samples (Fig. 1A). Accordingly, SARS-CoV-2 led to an extensive transcriptional response in the liver (Fig. 1B).

Differentially expressed genes

Finally, 5,147 and 5,122 genes were detected to have been downregulated and upregulated, respectively, in SARS-CoV-2 compared to healthy livers (Fig. 2A). Next, differentially expressed genes that were significantly downregulated were subjected to enrichment analysis based on the GO database. The 10 most significant pathways in both down- and up-regulated genes are listed in Table I.

Drug-gene interactions

Cytochromes in the livers of COVID-19 patients were examined and quarried. According to the results, 34 cytochromes of CYP2E1, CYP3A4, CYP2C9, CYP1A2, CYP2C8, CYP2A6, CYP4A11, CYP4F2, CYP4A22, CYP2C18, CYP8B1, CYP2A7, CYP4F3, CYP7A1, CYP2C19, CYP2B6, CYP1A1, CYP2D7, CYP4F11, CYP27A1, CYP3A43, CYP51A1, CYP4F22, CYP4F12, CYP3A5, CYP26A1, CYP39A1, CYP11A1, CYP4V2, CYP3A7, CYP17A1, CYP3A7, CYP3A7-CYP3A51P, and CYP21A2 were downregulated among the detected DEGs (Table II). In contrast, 4 cytochromes of CYP4B1, CYP2D6, CYP24A1, and CYP4F29P were upregulated.

The drug-gene interaction database (DGIdb) was quarried. As Table II shows, drugs related to these cytochromes were extracted. Besides, drug-gene interactions with the interaction score of higher than 1 were included.

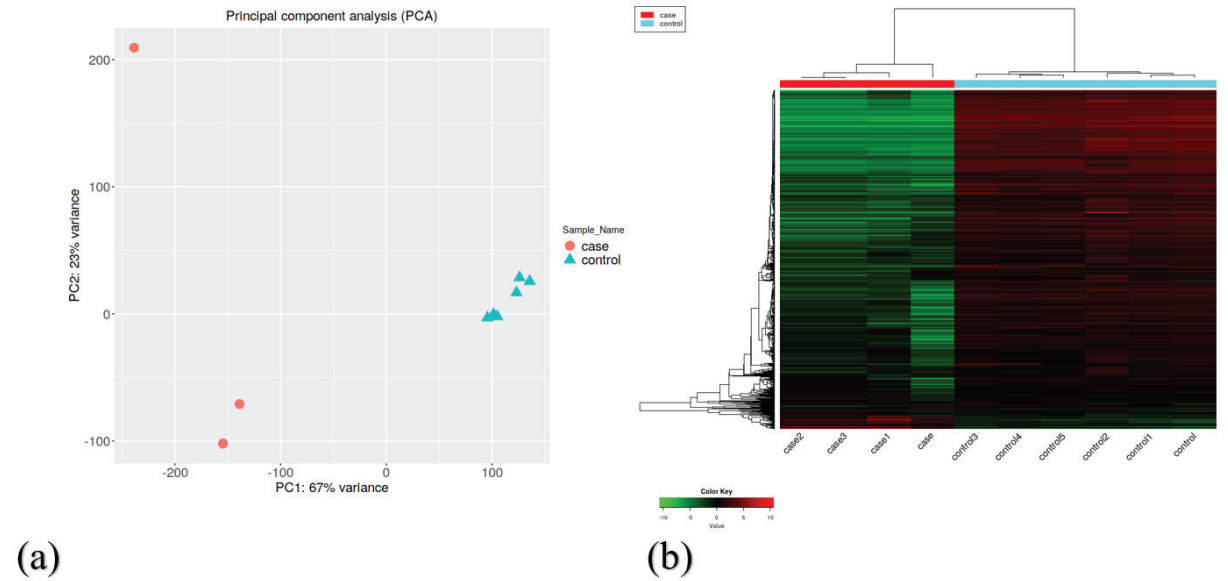

Fig. 1. (A) Principal components (PCA) analysis; (B) Heatmap diagram.

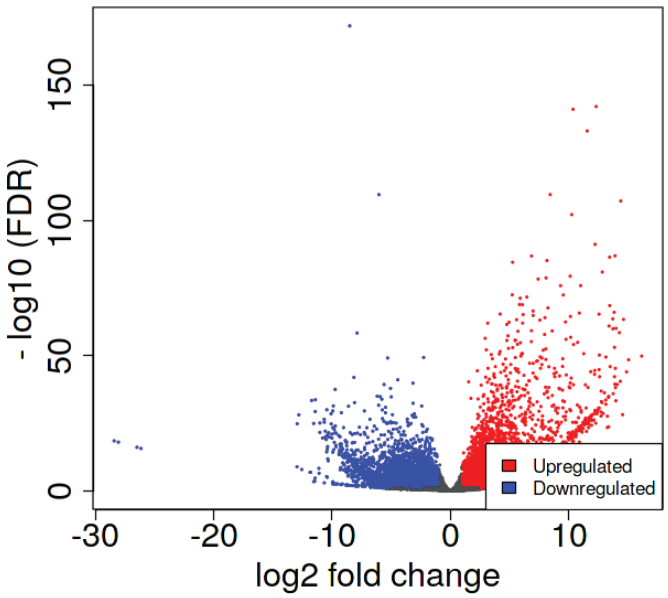

Fig. 2. (A) Volcano plot of differentially expressed genes.

TABLE I
GO DATABASE PATHWAY ENRICHMENT.

Upregulated			Downregulated		
Number of Genes	P-value	Number of Genes	Pathways	P-value	Number of Genes
Anatomical structure morphogenesis	6.3E-71	806	Small molecule metabolic process	2.7E-155	973
Movement of cells or subcellular component	1.3E-68	677	Organic acid metabolic process	7.1E-109	617
Locomotion	1.4E-57	587	Carboxylic acid metabolic process	7.1E-109	580
Circulatory system development	2.3E-55	387	Oxoacid metabolic process	1.6E-107	608
Biological adhesion	6.8E-54	505	Oxidation-reduction process	6.9E-104	552
Cell adhesion	2.1E-53	502	Catabolic process	9.4E-84	1049
Cell motility	2.1E-53	531	Organic substance catabolic process	9.1E-79	900
Cell migration	3.8E-52	487	Small molecule biosynthetic process	3.2E-76	386
Regulation of developmental process	4E-52	754	Lipid metabolic process	2.3E-75	643
Anatomical structure formation involved in morphogenesis	5.1E-51	393	Cellular catabolic process	3.1E-75	918

TABLE II
DRUG-GENE INTERACTIONS.

Symbol	log^2 Fold Change	Adjusted P-value	Drug name (Interaction Score) [reference]
CYP2E1	-16.15	1.70E-50	METACETAMOL (5.55) (10) VALERIAN (2.77) (11) PERFLUBRON(5.55)(12) PHENETHYL ISOCYANATE(5.55)(13) BRADANICLINE(1.39)(14) ISOFLAVONE(1.85)(15)
CYP3A4	-13.89	4.04E-40	–
CYP2C9	-13.35	3.14E-35	–
CYP1A2	-12.71	2.62E-28	–
CYP2C8	-12.55	1.67E-45	AMODIAQUINE (2.36) (16-17) CERIVASTATIN (1.77)(18-19)
CYP2A6	-11.84	1.01E-15	COUMARIN (4.21) (20) CAFFEINE (4.08) (21) LETROZOLE (9.57) (22) 3-FORMYLINDOLE (5.32) (23) CHEMBL1770735 (5.32) (24) IFOSFAMIDE (2.07) (25)
CYP4A11	-11.62	7.24E-39	SPIRONOLACTONE (1.68)[None found] AMILORIDE (2.13)[None found]
CYP4F2	-10.97	2.68E-24	ACENOCOUMAROL (23.92) (26) CLOPIDOGREL (1.2) [None found] PAFURAMIDINE MALEATE (7.97)[None found] PHENPROCOUMON (3.42)(27)
CYP4B1	+10.32	9.33E-12	THALIDOMIDE (1.82) (28-29)
CYP2D6	+6.322	1.77E-03	SPARTEINE(1.84)(30)
CYP24A1	+6.25	2.58E-02	LUNACALCIPOL (12.76) [None found] CHEMBL255088 (4.25) [None found] TELAPREVIR (4.25) (31) DEFERASIROX (3.83) (32) CALCITRIOL (2.32) (33)

DISCUSSION

This study showed that the function of the cytochrome P450 genes could get altered following COVID-19. A comparison of normal liver cells and SARS-CoV-2-infected hepatic cells showed a decreased expression level of some of the cytochrome P450 genes. Detoxification is a phenomenon that eliminates toxins from the body, which occurs in two phases. Accordingly, phase 1 is catalyzed by cytochrome p450. Products produced in phase 1 are mainly active oxygen and compounds causing damage to organs. These compounds are inactivated by phase 2 enzymes. More than 75% of detoxification occurs in the liver; however, it occurs in the intestinal mucosa in some cases.

According to Relats *et al.* (34), numerous food products react with cytochrome P450 enzyme-metabolized substances of DG-Idb. Quarries also showed significant inter-

actions with some nutrients, while its clinical significance is ambiguous.

Our search at DGIdb showed possible effects of COVID-19 on isoflavones, valerian, coumarin, and caffeine metabolism. Most of nutrients could be inhibitors of cytochromes. Accordingly, they reduce metabolic activity of the cytochrome P450 enzyme.

Medications listed in Table II were found to have interactions with cytochrome P450 enzymes. However, these results require further clinical research to confirm such interactions. Our results support the idea of disease-drug interactions in COVID-19 patients.

The most significant interactions were found to be those of CYP4F2 with acenocoumarol, with the interaction score of 23.92 followed by letrozole with the interaction score of 9.57.

On the other hand, with the advent of COVID-19, many people may seek herbal, supplementary, or dietary treatments as there is no definitive treatment for COVID-19 (11). Our study found some consistency with the in-vivo study of the Gurley *et al.* (11), which showed interactions of the black cohosh and valerian with human cytochromes of P450, 1A2, 2D6, 2E1, and 3A4/5 phenotypes.

Limitations of the study

While most similar control datasets were in non-alcoholic fatty liver disease, there could be some bias towards results of the study as non-alcoholic fatty liver may have different forms of gene expression with completely healthy samples. Besides, lots of confounding factors could be effective as results of various studies show that genetic polymorphisms might affect the body's response to COVID-19 (35,36).

The present study was a comprehensive analysis of COVID-19 disease-gene interactions that could contribute to adverse effects. The identified differentially expressing genes in this study might contribute to interactions with COVID-19 and present a drug-disease-interaction list to be considered for further realistic clinical research.

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