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Homozygosity for rs17775810 Minor Allele Associated With Reduced Mortality of COVID-19 in the UK Biobank Cohort

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Abstract. *Background/Aim: Adult outpatients with symptomatic COVID-19 treated with fluvoxamine, compared with placebo, had a lower likelihood of clinical deterioration over 15 days. Fluvoxamine strongly binds to the sigma-1 receptor (S1R) that regulates inflammation by inhibiting the production of cytokines, believed to be responsible for severe COVID-19. We evaluated the S1R locus on chr 9p13.3 in subjects tested positive for SARS-CoV-2. We focused on SNP rs17775810 that has been previously identified by examining loss-of-function mutations in the S1R gene associated with distal hereditary motor neuropathy. Patients and Methods: We utilized UK Biobank (UKB) data. Data processing was performed on Minerva, a Linux mainframe with Centos 7.6, at the Icahn School of Medicine at Mount Sinai. Results: The effect of rs17775810 genotype on survival was significant (p=0.036, 2 tailed Fisher exact test). The minor allele homozygotes (TT) had the lowest death rate (0%), whereas the non-TT genotypes (i.e. CT and CC) had the highest death rate (16.2%). Conclusion: The rs17775810 analysis corroborates the favorable effect of fluvoxamine on COVID-19 survival.*

In a preliminary study, adult outpatients with symptomatic COVID-19 treated with fluvoxamine, compared with placebo, had a lower likelihood of clinical deterioration over 15 days. Fluvoxamine strongly binds to the sigma-1 receptor (S1R) that regulates inflammation by inhibiting the production of cytokines, believed to be responsible for severe COVID-19 (1). The S1R receptor is a ubiquitously expressed endoplasmic reticulum (ER) chaperone protein located mainly at the ER membrane rather than predominantly on the plasma membrane of cells. The S1R receptor is expressed in many types of cells, not only immune cells, and can detach from the ER membrane and function in the ER lumen, chaperoning other proteins through the ER.

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Key Words: S1r, allele, fluvoxamine, COVID-19, motor neuropathy.

Patients and Methods

We utilized data from the UK Biobank (UKB). The UKB databases consist of data obtained from >500,000 community volunteers between 40-70 years of age at baseline (2006-2010), residing close to 22 assessment centers in the UK, Scotland and Wales. Baseline assessments on the database include demographics, the lifestyle of the subjects and the disease history of the subjects, with links available leading to electronic medical records. The UKB application for the present study was approved as UKB project 57245 (S.L. and P.H.R.) (2).

To investigate the relationship between S1R and COVID-19, we evaluated the S1R locus on chr 9p13.3 in subjects tested positive for SARS-CoV-2. We analysed the SNP rs17775810. This SNP has previously identified loss-of-function mutations in the S1R gene causing distal hereditary motor neuropathy (3) linked to an area including two SNPs: rs17775810, analyzed here, and one other not in UKB, which covered an area of 7.9 Mb. rs17775810 has a single nucleotide variation, C>T, with minor allele (T) frequency=0.21.

Data processing was performed on Minerva, a Linux mainframe with Centos 7.6, at the Icahn School of Medicine at Mount Sinai. We used PLINK, a whole-genome association analysis toolset, to process the UKB chromosome 9 files, and the UK Biobank Data Parser (ukbb parser), a python-based package that allows easy interfacing with the large UKB dataset (4).

Results

We evaluated the association of the rs17775810 genotypes with survival of COVID-19 patients and designated the major rs17775810 allele as C and the minor allele as T. We analyzed data from 688 UKB subjects with laboratory confirmed COVID-19, 49% female, 51% male. The mean

age was 54±9.2 (mean±SD). One hundred eight (16%) had died of COVID-19. Among the subjects, 83% were white British, 3% were Irish, 3% were of any other white background, 2% were African, 2% were Caribbean, 7% were of other ethnicity.

COVID-19 survival according to the different genotypes (TT homozygote *versus* non-TT) is shown in Table I. The effect of each genotype on survival was significant (p=0.036, 2 tailed Fisher exact test). The TT homozygotes had the lowest death rate (0%), whereas the non-TT genotypes (*i.e.* CT and CC) had the highest death rate (16.2%).

COVID-19 survival according to the rs17775810 genotype (TT *versus* CT and CC) is shown in Table II. The TT homozygotes had the lowest death rate (0%, p=0.020, likelihood ratio).

Table I. *COVID-19 patient survival according to the rs17775810 genotype (TT versus non-TT) in 688 UKB subjects. The effect of genotype on survival was significant (p=0.036, 2 tailed Fisher exact test). The TT homozygotes had the lowest death rate (0%), whereas the non-TT genotypes (i.e. CT and CC) had the highest death rate (16.2%).*

Genotype	Alive	Died	% Died
Non-TT	557	108	16.2
TT	23	0	0

Table II. *COVID-19 patient survival according to the rs17775810 genotype (TT versus CT and CC) in 688 UKB subjects (p=0.020, likelihood ratio).*

Genotype	Alive	Died	% Died
CC	361	66	15.5
CT	196	42	17.6
TT	23	0	0

Discussion

Genome-wide association studies have found multiple genes and loci that increase the risk of respiratory failure in COVID-19 (5). One locus on chromosome 3p21.31 contains 6 genes involved in inflammation (*SLC6A20, LZTFL1, CCR9, FYCO1, CXCR6*, and *XCR1*) (5).

The ABO gene, chr 9q34.2, which determines blood type, may affect disease severity. Corrected for age and sex, a higher risk for respiratory failure was found among persons with blood group A than among patients with other blood groups, and a protective effect for blood group O as compared with the other blood groups (5). However, this result has not been reproduced. A UK study of 2200 COVID-19 patients found no relationship of ABO blood type with disease severity (6). A Danish study identified ABO blood group as a risk factor for SARS-CoV-2 infection but not for hospitalization or death from COVID-19 (7).

We examined the association of rs17775810 genotypes with the survival of COVID-19 patients. We found that individuals homozygous for the rs17775810 minor allele (TT) have a lower death rate. This result is consistent with another study on SARS-CoV that examined the effect of a polymorphism in CLEC4M, which encodes L-SIGN, a SARS-CoV binding receptor (8). It was shown that homozygosity for *CLEC4M* tandem repeats played a protective role in SARS coronavirus infection. This effect was not observed in heterozygotes (9).

It has been shown that fluvoxamine can prevent clinical deterioration of COVID-19 patients (1). It is not known whether this effect of fluvoxamine is due to actions on immune cells *versus* other types of cells. There are in fact several different hypothesized mechanisms by which fluvoxamine might act. Some involve S1R receptor binding, but others do not (8, 10-14).

Our rs17775810 analysis suggests that the favorable effect of fluvoxamine on survival, as reported by Lenze *et al.* (1), may be mediated through S1R receptor.

A weakness of our study is that rs17775810, a common SNP, has no known functional significance and is not within the S1R gene or within any other known gene. S1R starts at chr9p 34,634,722 bp, ends at 34,637,809 bp; rs17775810 is at 30,504,350. We were able to examine one SNP within S1R, rs11559048, but the minor allele frequency (0.002) was too low to produce meaningful statistics. There are four other SNPs within S1R (15), but the UKB had no data on them, nor did we have whole exome sequencing data. Further studies are warranted.

Conflicts of Interest

The Authors report no conflicts of interest in relation to this study.

Authors' Contributions

Dr. Lehrer and Dr. Rheinstein contributed equally to the conception, writing, and data analysis of this study.

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