Clinical Section: Letter to the Editor

Apolipoprotein E4 Allele in Subjects with COVID-19

Jaroslav Alois Hubacek[a, b]   Lucie Dlouha[a, c]   Ladislav Dusek[d, e]   Ondrej Majek[d, e]
Vera Adamkova[f, g]

[a]Experimental Medicine Centre, Institute for Clinical and Experimental Medicine, Prague, Czech Republic;
[b]Third Department of Internal Medicine, First Faculty of Medicine, Charles University, Prague, Czech Republic;
[c]Department of Anthropology and Human Genetics, Faculty of Science, Charles University, Prague, Czech Republic;
[d]Institute of Health Information and Statistics of the Czech Republic, Prague, Czech Republic; [e]Institute of
Biostatistics and Analyses, Faculty of Medicine, Masaryk University, Brno, Czech Republic; [f]Department of Preventive
Cardiology, Institute for Clinical and Experimental Medicine, Prague, Czech Republic; [g]Department of Nephrology,
First Faculty of Medicine, Charles University, Prague, Czech Republic

Dear Editor,

We recently read with keen interest a study by Del Ser et al. [1], who suggest that carriers of *APOE4* alleles come under increased risk of mild to moderate symptoms of coronavirus disease 2019 (COVID-19) during SARS-CoV-2 infection. COVID-19 disease occurs as a consequence of infection with the RNA coronavirus SARS-CoV-2. First reported in Wuhan, China, in December 2019, COVID-19 has since spread rapidly and has become a global pandemic [2]. Although highly contagious, the virus is nonetheless associated with relatively low mortality when compared with other coronavirus infections (MERS or SARS).

Apolipoprotein E (APOE, OMIM acc. ID – 107741, Gene ID – 348) is a small protein that plays an important role predominantly in lipid metabolism and cholesterol homeostasis. The 3 most common *APOE* alleles differ based on a single amino acid exchange as follows: *APOE2* (Cys112, Cys158 – rs7412), *APOE3* (Cys112 and Arg158), and *APOE4* (Arg112 – rs429358, Arg158). *APOE3* is the most common allele worldwide, exhibiting a population frequency of approximately 65–85%. The ancestral allele *APOE4*, generally considered deleterious, is a significant risk factor for Alzheimer's disease and is also associated with atherosclerotic cardiovascular disease [3].

Using RT-PCR and the TaqMan assay (ID – C_3084793_20), we analysed the *APOE4* polymorphism (rs429358) in a group of 408 Czech first-wave (approximately March 2020–June 2020) SARS-CoV-2 PCR-positive (PCR test) subjects (54.7% females, mean age 44 ± 15 years, diabetes prevalence 7.8%, hypertension prevalence 13.3%). Of this total number, 164 were asymptomatic and 244 symptomatic [4]. All patients were confirmed SARS-CoV-2-negative by the time of sample collection in July 2020. For comparison purposes, we consulted *APOE4+* genotype (*APOE4/E4, APOE4/E3,* and *APOE4/E2*) frequencies in a large population-based cohort from the Czech part of post-MONICA study ($N = 2,606$; 53.6% females, mean age 48 ± 11 years, diabetes prevalence 8.2%, hypertension prevalence 22.3%) [5]. Information on COVID-19 status was not available for these subjects.

Detailed genotype frequencies are given in Table 1. We found no significant differences between the entire group of SARS-CoV-2-positive subjects and the control population (χ^2 test; $p = 0.11$). However, after applying disease status (asymptomatic and symptomatic subjects were

Correspondence to:
Jaroslav A. Hubacek, jahb@ikem.cz

Table 1. Distribution of APOE4 allele carriers in controls and SARS-CoV-2-positive subjects

APOE	Post-MONICA		COVID-19 asymptomatic		COVID-19 symptomatic		OR (95% CI) controls versus asymptomatic	p value	OR (95% CI) controls versus symptomatic	p value
	N	%	N	%	N	%				
	2,606		164		244					
E4/E4	33	1.3	0	0	5	2.0	N/A	N/A	1.75 (0.67–4.52)	0.25
E4/EX	442	17.0	29	15.4	54	22.1	0.97 (0.64–1.46)	0.87	1.47 (1.02–1.94)	**0.04**
Other	2,131	81.7	135	84.6	185	75.8	1.00		1.00	
+E4	475	18.3	29	15.4	59	24.1	0.96 (0.64–1.46)	0.86	1.43 (1.05–1.95)	**0.03**
Other	2,131	81.7	135	84.6	185	75.8	1.00		1.00	

EX, APOE3 or APOE2 allele; OR, odds ratio; CI, confidence interval; COVID-19, coronavirus disease 2019; APOE, apolipoprotein E. p value calculated using the χ^2 test. Values in bold indicate significance.

separately compared with the control population) to our model, the frequency of carriers of at least one *APOE4* allele was significantly higher in symptomatic COVID-19 subjects than in controls (p = 0.03; OR, 95% CI – 1.43, 1.05–1.95). In contrast, genotype frequencies were almost identical in COVID-19-asymptomatic (SARS-CoV-2-positive) subjects and in the control group population (p = 0.86).

Intriguingly, possible associations between the *APOE* polymorphism and COVID-19 have been mentioned before the study by Del Ser et al. [1] and our study have been performed. Theoretically, this idea was briefly elaborated by Goldstein et al. [6], based on the fact that the *APOE4* allele is known to be more common in black Africans (population frequency: ~30–40%) than Caucasians (population frequency ~7–20%) and Asians (population frequency: ~5–15%) [7]. It has also been reported that the same ethnicity is affected by higher COVID-19 prevalence and mortality than other ethnic groups [8]. In fact, hundreds of SNPs have been shown to exhibit significant allelic differences (e.g., variants within the genes for apolipoprotein L1, alcohol dehydrogenase, and HFE) between ethnicities. Interestingly, however, none of these have been identified as potential predictors of COVID-19 severity using a GWAS approach. As such, ethnic differences per se are probably important for focusing, but insufficient at determining the genetic characteristics of COVID-19 candidate genes.

Importantly, based on a recent analysis of the UK Biobank Community Cohort, *APOE* polymorphism was found to have a considerable effect on COVID-19 severity [9]. The authors reported that carriers of *APOE4E4* homozygotes were at increased risk of severe COVID-19, even after excluding individuals with diabetes, cardiovascular disease, and hypertension.

These findings underline the extreme pleiotropic complexity of the *APOE* gene (or possibly some adjacent – clustering genes with variants in high linkage disequilibrium with the *APOE4* allele). APOE is expressed in almost all human tissues, and its fundamental role in lipid transport is important for many functions, including immunity [10]. Further supporting the findings of the independent studies cited above, the results of our study indicate that the *APOE4* allele is linked to increased risk of symptomatic COVID-19, making *APOE* the first gene to be associated with symptomatic COVID-19 disease directly in several independent studies.

Statement of Ethics

All subjects provided their written informed consent with the participation in the study. The study protocol (which is in agreement with Helsinki declaration of 1975) has been approved by the Multicentre Ethics Committee at the Institute of Biostatistics and Analyses, Faculty of Medicine, Masaryk University, Brno, Czech Republic (protocol ID – 01-110520/EK).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

J.A.H. – funding, supervision, and writing major part of the manuscript. L.Dl. – data collection and genotype analysis. L.Du. – funding and supervision. O.M. – supervision, data collection, and interpretation. V.A. – funding, data interpretation, and supervision. All authors participated in designing the study protocol, interpreting the results, revising, and approving the final text.

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