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LETTER TO THE EDITOR

Association of ApoE isoforms with COVID-19 outcomes: a world-wide epidemiological study

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To the Editor,

Recent studies in UK Cohort [1, 2] documenting increased COVID-19 incidence and deaths in populations homozygous for apolipoprotein E (ApoE) $\varepsilon_4/\varepsilon_4$ isoforms compared to $\varepsilon_3/\varepsilon_3$ with heightened significance is apprehensive. Furthermore, increased susceptibility of $\varepsilon_4/\varepsilon_4$ brain cells to SARS-CoV-2 infection in vitro [3] define its possible causal association for COVID-19 outcomes including neurological defects. However, distribution of ApoE isoforms vary amongst populations and their definitive robust association beyond UK cohort is still unknown. This tempted us to conduct a world-wide genetic association study of ApoE isoforms with COVID-19 outcomes.

Literature search on PubMed and Google scholars was conducted to retrieve ApoE isoforms data from healthy control across different countries of global population from relevant published papers. Papers with insufficient data and/or country name were excluded. Available data were subjected to Hardy Weinberg Equilibrium (HWE). Data showing deviation were excluded from analysis. Data pooling was carried out when more than one data sets were available for a particular country. Country wise frequency of all three ApoE isoforms (ε_2, ε_3 and ε_4) were determined. COVID-19 data (incidence and deaths per millions of population) accessed on 16th January, 2021 from worldometer site (https://www.worldometers.info/coronavirus/) were associated with frequency distribution of different ApoE isoforms by Spearman's correlation coefficient analysis in GraphPad Prism (version 5.0). Data of 16th January, 2021 (latest available before massive vaccination drive) was used to nullify the possible confounding effect due to vaccination disparity across the countries. A p value < 0.05 was considered significant.

ApoE data of 103,414 healthy controls from 228 studies belonging to 66 countries were finally enrolled which showed varied ranges of distribution for ε_2 (0.625–19.1%), ε_3 (52.09–92.57%) and ε_4 (4.45–28.59%) (S1). Correlation analysis revealed significant but weak inverse relationship of ε_4 allele with COVID-19 susceptibility ($p=0.033$, Spearman's $r=-0.263$). Correlation analysis of ApoE alleles with COVID-19 morbidity and mortality was conducted separately for populations of different genetic ancestry (such as Asia, Africa, America and Europe). Consistently, ε_4 allele was negatively correlated with COVID-19 outcomes (for incidence: $p=0.0181$, $r=-0.6$; for deaths: $p=0.0078$ and $r=-0.6571$) in Asia, only. Interestingly, a significant positive correlation was observed between ε_3 allele frequency and COVID-19 outcomes (for incidence: $p=0.0045$ and $r=0.689$; for deaths: $p=0.0011$ and $r=0.757$) in Asia, whereas in Europe, this association reached to significant level with mortality ($p=0.048$, $r=0.383$) only. None of the alleles were found to be correlated with COVID-19 outcomes in Africa and America (Table 1).

Contrasting to UK cohort [1, 2], we did not observe ε_4 isoform as the risk factor of COVID-19 even in Europeans. Since, UK cohort were older age population and had comorbidities, they were more vulnerable to COVID-19. Furthermore, complete exclusion of individuals having one or more of the comorbidities being not done, COVID-19 risk in $\varepsilon_4/\varepsilon_4$ should not be proclaimed as independent to pre-existing ApoE e4 associated comorbidities. Our study which includes apparently healthy control from across the world of all age groups negates the impact of comorbidity, though age groups stratified association of ApoE isoforms with COVID-19 could not be performed as age distribution of genotypes data were not available. Moreover, our findings of inconsistency in associations of ApoE variants with COVID-19 outcomes should not be surprised, since the distribution of ApoE isoforms widely vary across populations

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Table 1 Association of ApoE isoforms with COVID-19 outcomes

ApoE isoforms/ populations	ε_2		ε_3		ε_4	
	C/M	D/M	C/M	D/M	C/M	D/M
Asia ($N=15$)	0.458	0.226	0.0045 (0.689)	0.0011 (0.757)	0.0181 (− 0.6)	0.0078 (− 0.6571)
Africa ($N=10$)	0.260	0.293	0.803	0.803	0.777	0.726
America ($N=13$)	0.437	0.312	0.816	0.958	0.654	0.689
Europe ($N=27$)	0.946	0.765	0.112	0.048 (0.383)	0.434	0.338
Total ($N=66$)[a]	0.458	0.913	0.129	0.104	0.033 (− 0.263)	0.107

Values inside the box are p value. Spearman's correlation coefficient values (+ for positive correlation and − for negative correlation) are given in parentheses for which a significant p value of < 0.05 is observed

C/M cases/millions, *D/M* deaths/millions, *N* number of studies

[a]Include additional one data set from Australia

and that functionality of these isoforms are shown to be dependent on their race/ethnicity specific linkage disequilibrium (LD) and complex interactions with other genetic variants in ApoE clusters [4]. The underlying differences in association of ApoE isoforms in the present study can be explained by similar population specific heterogenous effects of ApoE isoforms. Therefore, definitive association of ApoE isoforms towards COVID-19 outcomes is challenging and seems to be more complex. The fact that angiotensin-converting enzyme 2 (ACE2) (an important host receptor for SARS-Cov2 infection and one of the several determinants for population variability of COVID-19 outcomes) and ApoE co-express in lungs alveolar cells [5], the main target for SARS-Cov2 infection. Interestingly, presence or absence of ACE2 in ApoE knockout mice is described to modulate ApoE related altered physiology [3, 6, 7]. However, such connection between ACE2 and ApoE are yet to be established in COVID-19. We hypothesize that population specific variable expression of ACE2 and other relevant genes in ApoE clusters may affect association of ApoE isoforms towards COVID19 outcomes. Therefore, well designed observational studies across various populations of different genetic backgrounds are sought to establish a definitive role of ApoE in COVID19.

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Declarations

Conflict of interest All authors declare no conflict of interest.

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