

## Letter to the Editor

# The ApoE Locus and COVID-19: Are We Going Where We Have Been?

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Four decades ago in 1985, alleles of apolipoprotein E (ApoE)  $\epsilon 2/\epsilon 3/\epsilon 4$  became famous for explaining 16% of genetic variance in low-density lipoprotein cholesterol in the benchmark study of Sing and Davignon (1): total blood cholesterol, low-density lipoprotein cholesterol, and apolipoprotein B were elevated by ApoE  $\epsilon 4$  (ApoE4) allele and lowered by ApoE  $\epsilon 2$  (ApoE2). The adverse associations of ApoE4 with atherosclerosis and cardiovascular disease (CVD) (1) were extended to shortened longevity in 1987 (2) and then to risk of Alzheimer disease (AD) in 1993 (3). The next year, ApoE2 was associated with lower incidence of AD and greater longevity (4,5). ApoE is synthesized body-wide in adipocytes, hepatocytes, brain astrocytes, and arterial wall macrophages with local roles in lipid transport that are critical for brain, immune, and vascular functions.

ApoE4 is the ancestral human gene (6,7) from which ApoE3 and then ApoE2 evolved in the last 250 000 years (8). The persistence of ApoE4 was hypothesized to be advantageous for lipophilic pathogens (9). In fact, apoE4 benefits hepatitis C infections (10), as well as survival in highly infectious environments (11) and cognitive functions (12,13).

This year, the ApoE locus has shown a new face with the increased vulnerability of ApoE4 carriers to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), particularly for later ages. We briefly summarize how pleiotropies of ApoE4 may mediate multiple morbidities that increase vulnerability, and consider genes in the ApoE cluster that may contribute to age-related host susceptibility.

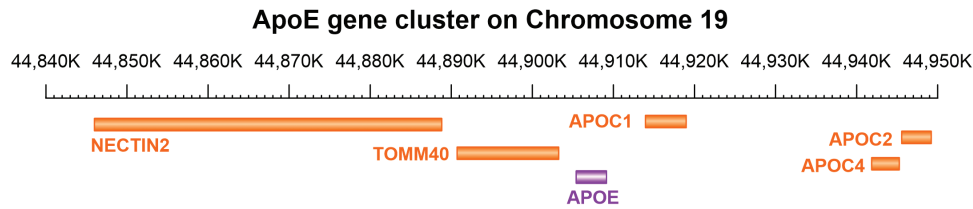
## Complex Genetics of the ApoE Locus

Preexisting morbidities increase risk of COVID-19 infections and mortality: for young adults: diabetes and obesity; for older people: diabetes and dementia (14,15). COVID-19 also damages the cardiovascular system with atrial fibrillation, ventricular arrhythmia, and disseminated coagulation (16). These morbidities are also

associated with variants in the ApoE gene cluster that we hypothesize are relevant to COVID-19. ApoE4 homozygotes have 2.2-fold higher risk for COVID-19 positivity and 4.3-fold more case-fatality after COVID-19 than ApoE3 homozygotes (17,18). Heterozygosity ( $\epsilon 3/\epsilon 4$ ) was modestly associated with COVID-19 below linear dose dependence. Strong associations for  $\epsilon 4/\epsilon 4$  with COVID-19 were not diminished by excluding dementia, hypertension, coronary heart disease (CHD), or type II diabetes. Based on these associations, Kuo et al. hypothesize that ApoE4 has recessive effects on COVID-19 outcomes and suggest that these effects are independent of these common age-related diseases. We discuss how ApoE allele pleiotropies can mediate COVID-19 infectivity and survival.

The multiple ApoE alleles of humans are unique among primates, which are monomorphic for an ApoE protein that shares the R112 and R158 of human ApoE4 (12). Unlike the hemoglobin variant relationship to malaria resistance, the wide variations of ApoE4 (eg, 3-fold gradient from Mediterranean to Nordic countries) has not been linked to past environments. The ApoE locus has complex linkage disequilibrium (LD) structures (19,20), differing by race/ethnic groups (21,22). The variable AD risks suggest that ApoE be considered a “major gene” rather than “risk gene” (23). We may consider complex haplotypes rather than single alleles predisposing to age-related diseases.

Associations of ApoE with AD also involve the neighboring TOMM40 poly-thymine repeat polymorphism (rs10524523) in the “ApoE gene cluster” CH19q13 (Figure 1), which can increase susceptibility to AD either independently, or in cis-combination with ApoE4 (24,25). Additionally, AD risks are increased by the haplotype of ApoE (rs405509\_T and ApoE4) when both are in cis on the same chromosome (26). Several complex haplotypes in the APOE gene cluster can alter AD risk independently of ApoE4 (27). We hypothesize that ApoE4 associations with COVID-19 extend to the ApoE gene complex with balancing detrimental and protective



**Figure 1.** ApoE and neighboring genes in the human ApoE gene cluster on chromosome 19q13.32. This locus of more than 20 named genes shows extensive conservation in mammals; in rodents, the order is reversed (inverted synteny).

effects in haplotypes, and multiple gene-by-gene transcriptional interactions (28). This approach could identify protective genes for COVID-19. ApoE2 also merits consideration in COVID-19, given its benefit to CVD and AD.

CH19q13.13 includes other apolipoprotein genes, ApoC1–ApoC4–ApoC2 (29). ApoC1 was first known for inhibiting cholesteryl ester transfer protein (CETP) (30). Diabetes can impair ApoC1 functions (31), as does CVD with dyslipidemia (32). ApoC4 also mediates triglyceride metabolism (33). Genome-wide association studies showed that ApoC1–ApoC4–ApoC2 modulate triglycerides and high-density lipoproteins (34). Pleiotropies of ApoE alleles for dietary lipid absorption and uptake by fat, muscle, and brain cells (35) could include ApoC haplotypes.

### Roles of ApoE in Viral Infections

Cell infection by SARS-Cov-2 is mediated by binding to ACE2 (angiotensin-converting enzyme 2), which is also a key component of the renin–angiotensin system (RAS) in blood pressure regulation. The cell types expressing ACE2 show relationships to organ pathology, and include intestinal epithelia, lung alveoli (36), myocardial pericytes (37), and nasal epithelial (38). Drug candidates for SARS-Cov-2 protection include several senolytics that interact with ACE2 and CD26, another host receptor (39,40).

Infections may involve indirect roles of ApoE alleles. Hepatitis virus C binds to the ApoE protein (41). We ask, could ApoE also bind coronaviruses? Several ApoE cluster genes may interact with COVID-19, for example, *NECTIN2* (herpes receptor HHV1) and *ApoC1* which, like ApoE, is in the HCV envelope (42). Neighboring genes mediate inflammation (C5a receptor, IGFL1, RELB, TGF $\beta$ ). Alzheimer disease risk haplotypes include ApoE and *NECTIN2* SNPs (19). ApoE cluster haplotypes associate with the same morbidities from CVD and obesity (43,44) that increase vulnerability to COVID-19.

### Conclusions

The ApoE trail, like a Moebius strip, takes us back to where we started from 4 decades ago with another view. To understand how ApoE4 may increase COVID-19 infectivity and mortality and possible haplotypes or interactions, we have returned to the original associations of ApoE variants with blood lipids, vascular disease, and cognition. The ApoE trail has expanded beyond a single gene locus to engage adjacent genes in the ApoE gene cluster that also modulate CVD and AD, as well as viral infections.

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