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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) ε2/ε3/ε4 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 ε4 (ApoE4) allele and lowered by ApoE ε2 (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 (ε3/ε4) was modestly associated with COVID-19 below linear dose dependence. Strong associations for ε4/ε4 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

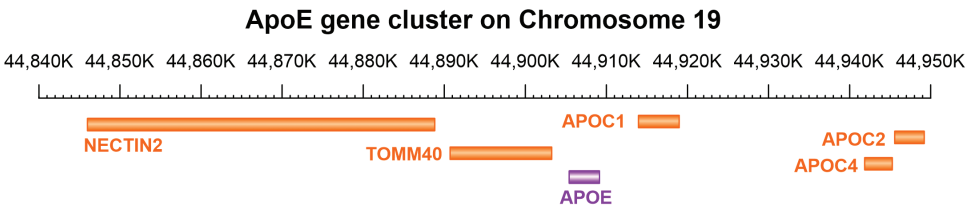

Figure 1. ApoE and neighboring genes in the human ApoE gene cluster on chromosome 19q13.32. This locus of more than 20 named genes shows extensive conservation in mammals; in rodents, the order is reversed (inverted synteny).

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.

CH19q19.13 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 SARC-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, TGFβ). 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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References

1. Sing CF, Davignon J. Role of the apolipoprotein E polymorphism in determining normal plasma lipid and lipoprotein variation. *Am J Hum Genet*. 1985;37:268–285.
2. Davignon J, Bouthillier D, Nestruck AC, Sing CF. Apolipoprotein E polymorphism and atherosclerosis: insight from a study in octogenarians. *Trans Am Clin Climatol Assoc*. 1988;99:100–110.
3. Strittmatter WJ, Weisgraber KH, Huang DY, et al. Binding of human apolipoprotein E to synthetic amyloid beta peptide: isoform-specific effects and implications for late-onset Alzheimer disease. *Proc Natl Acad Sci U S A*. 1993;90:8098–8102. doi:10.1073/pnas.90.17.8098
4. Corder EH, Saunders AM, Risch NJ, et al. Protective effect of apolipoprotein E type 2 allele for late onset Alzheimer disease. *Nat Genet*. 1994;7:180–184. doi:10.1038/ng0694-180
5. Schächter F, Faure-Delanef L, Guénot F, et al. Genetic associations with human longevity at the APOE and ACE loci. *Nat Genet*. 1994;6:29–32. doi:10.1038/ng0194-29
6. Hanlon CS, Rubinsztein DC. Arginine residues at codons 112 and 158 in the apolipoprotein E gene correspond to the ancestral state in humans. *Atherosclerosis*. 1995;112:85–90. doi:10.1016/0021-9150(94)05402-5
7. Finch CE, Sapolsky RM. The evolution of Alzheimer disease, the reproductive schedule, and apoE isoforms. *Neurobiol Aging*. 1999;20:407–428. doi:10.1016/s0197-4580(99)00053-6
8. Fullerton SM, Clark AG, Weiss KM, et al. Apolipoprotein E variation at the sequence haplotype level: implications for the origin and maintenance of a major human polymorphism. *Am J Hum Genet*. 2000;67:881–900. doi:10.1086/303070
9. Martin GM. APOE alleles and lipophylic pathogens. *Neurobiol Aging*. 1999;20:441–443. doi:10.1016/s0197-4580(99)00078-0
10. Wozniak MA, Itzhaki RF, Faragher EB, James MW, Ryder SD, Irving WL; Trent HCV Study Group. Apolipoprotein E-epsilon 4 protects against severe liver disease caused by hepatitis C virus. *Hepatology*. 2002;36:456–463. doi:10.1053/jhep.2002.34745
11. van Exel E, Koopman JJE, Bodegom DV, et al. Effect of APOE ε4 allele on survival and fertility in an adverse environment. *PLoS One*. 2017;12:e0179497. doi:10.1371/journal.pone.0179497
12. Trumble BC, Finch CE. The exposome in human evolution: from dust to diesel. *Q Rev Biol*. 2019;94:333–394. doi:10.1086/706768
13. Mitter SS, Oriá RB, Kvalsund MP, et al. Apolipoprotein E4 influences growth and cognitive responses to micronutrient supplementation in shantytown children from northeast Brazil. *Clinics (Sao Paulo)*. 2012;67:11–18. doi:10.6061/clinics/2012(01)03
14. Atkins JL, Masoli JAH, Delgado J, et al. Preexisting comorbidities predicting COVID-19 and mortality in the UK Biobank community cohort. *J Gerontol A Biol Sci Med Sci*. 2020. doi:10.1093/gerona/glaa183
15. Kass DA, Duggal P, Cingolani O. Obesity could shift severe COVID-19 disease to younger ages. *Lancet*. 2020;395:1544–1545. doi:10.1016/S0140-6736(20)31024-2
16. Guzik TJ, Mohiddin SA, Dimarco A, et al. COVID-19 and the cardiovascular system: implications for risk assessment, diagnosis, and treatment options. *Cardiovasc Res*. 2020;116:1666–1687. doi:10.1093/cvr/cvaa106
17. Kuo CL, Pilling LC, Atkins JL, et al. APOE e4 genotype predicts severe COVID-19 in the UK Biobank community cohort. *J Gerontol A Biol Sci Med Sci*. 2020. doi:10.1093/gerona/glaa131

18. Kuo CL, Pilling LC, Atkins JL, et al. ApoE e4e4 genotype and mortality with COVID-19 in UK Biobank. *J Gerontol A Biol Sci Med Sci*. 2020. doi:10.1093/gerona/glaa169
19. Kulminski AM, Shu L, Loika Y, et al. Genetic and regulatory architecture of Alzheimer's disease in the APOE region. *Alzheimers Dement (Amst)*. 2020;12:e12008. doi:10.1002/dad2.12008
20. Yu CE, Seltman H, Peskind ER, et al. Comprehensive analysis of APOE and selected proximate markers for late-onset Alzheimer's disease: patterns of linkage disequilibrium and disease/marker association. *Genomics*. 2007;89:655–665. doi:10.1016/j.ygeno.2007.02.002
21. Takei N, Miyashita A, Tsukie T, et al.; Japanese Genetic Study Consortium for Alzheimer Disease. Genetic association study on in and around the APOE in late-onset Alzheimer disease in Japanese. *Genomics*. 2009;93:441–448. doi:10.1016/j.ygeno.2009.01.003
22. Kulminski AM, Shu L, Loika Y, et al. APOE region molecular signatures of Alzheimer's disease across races/ethnicities. *Neurobiol Aging*. 2020;87:141.e1–141.e8. doi:10.1016/j.neurobiolaging.2019.11.007
23. Genin E, Hannequin D, Wallon D, et al. APOE and Alzheimer disease: a major gene with semi-dominant inheritance. *Mol Psychiatry*. 2011;16:903–907. doi:10.1038/mp.2011.52
24. Roses AD, Lutz MW, Amrine-Madsen H, et al. A TOMM40 variable-length polymorphism predicts the age of late-onset Alzheimer's disease. *Pharmacogenomics J*. 2010;10:375–384. doi:10.1038/tpj.2009.69
25. Lutz MW, Crenshaw D, Welsh-Bohmer KA, Burns DK, Roses AD. New genetic approaches to AD: lessons from APOE-TOMM40 phylogenetics. *Curr Neurol Neurosci Rep*. 2016;16:48. doi:10.1007/s11910-016-0643-8
26. Lescai F, Chiamenti AM, Codemo A, et al. An APOE haplotype associated with decreased ε4 expression increases the risk of late onset Alzheimer's disease. *J Alzheimers Dis*. 2011;24:235–245. doi:10.3233/JAD-2011-101764
27. Zhou X, Chen Y, Mok KY, et al. Non-coding variability at the APOE locus contributes to the Alzheimer's risk. *Nat Commun*. 2019;10:3310. doi:10.1038/s41467-019-10945-z
28. Bergman A, Atzmon G, Ye K, MacCarthy T, Barzilai N. Buffering mechanisms in aging: a systems approach toward uncovering the genetic component of aging. *PLoS Comput Biol*. 2007;3:e170. doi:10.1371/journal.pcbi.0030170
29. Scott J, Knott TJ, Shaw DJ, Brook JD. Localization of genes encoding apolipoproteins CI, CII, and E to the p13—cen region of human chromosome 19. *Hum Genet*. 1985;71:144–146. doi:10.1007/BF00283370
30. Gautier T, Masson D, de Barros JP, et al. Human apolipoprotein C-I accounts for the ability of plasma high density lipoproteins to inhibit the cholesteryl ester transfer protein activity. *J Biol Chem*. 2000;275:37504–37509. doi:10.1074/jbc.M007210200
31. Bouillet B, Gautier T, Blache D, et al. Glycation of apolipoprotein C1 impairs its CETP inhibitory property: pathophysiological relevance in patients with type 1 and type 2 diabetes. *Diabetes Care*. 2014;37:1148–1156. doi:10.2337/dc13-1467
32. Pillois X, Gautier T, Bouillet B, et al. Constitutive inhibition of plasma CETP by apolipoprotein C1 is blunted in dyslipidemic patients with coronary artery disease. *J Lipid Res*. 2012;53:1200–1209. doi:10.1194/jlr.M022988
33. Allan CM, Taylor JM. Expression of a novel human apolipoprotein (apoC-IV) causes hypertriglyceridemia in transgenic mice. *J Lipid Res*. 1996;37:1510–1518.
34. Willer CJ, Schmidt EM, Sengupta S, et al.; Global Lipids Genetics Consortium. Discovery and refinement of loci associated with lipid levels. *Nat Genet*. 2013;45:1274–1283. doi:10.1038/ng.2797
35. Yassine HN, Finch CE. APOE alleles and diet in brain aging and Alzheimer's disease. *Front Aging Neurosci*. 2020;12:150. doi:10.3389/fnagi.2020.00150
36. Divani AA, Andalib S, Di Napoli M, et al. Coronavirus disease 2019 and stroke: clinical manifestations and pathophysiological insights. *J Stroke Cerebrovasc Dis*. 2020;29:104941. doi:10.1016/j.jstrokecerebrovasdis.2020.104941
37. Chen L, Li X, Chen M, Feng Y, Xiong C. The ACE2 expression in human heart indicates new potential mechanism of heart injury among patients infected with SARS-CoV-2. *Cardiovasc Res*. 2020;116:1097–1100. doi:10.1093/cvr/cvaa078
38. Bilinska K, Jakubowska P, Von Bartheld CS, Butowt R. Expression of the SARS-CoV-2 entry proteins, ACE2 and TMPRSS2, in cells of the olfactory epithelium: identification of cell types and trends with age. *ACS Chem Neurosci*. 2020;11:1555–1562. doi:10.1021/acschemneuro.0c00210
39. Sargiacomo C, Sotgia F, Lisanti MP. COVID-19 and chronological aging: senolytics and other anti-aging drugs for the treatment or prevention of corona virus infection? *Aging (Albany NY)*. 2020;12:6511–6517. doi:10.18632/aging.103001
40. McKee DL, Sternberg A, Stange U, Laufer S, Naujokat C. Candidate drugs against SARS-CoV-2 and COVID-19. *Pharmacol Res*. 2020;157:104859. doi:10.1016/j.phrs.2020.104859
41. Jiang J, Wu X, Tang H, Luo G. Apolipoprotein E mediates attachment of clinical hepatitis C virus to hepatocytes by binding to cell surface heparan sulfate proteoglycan receptors. *PLoS ONE*. 2013;8:e67982. doi:10.1371/journal.pone.0067982
42. Fuior EV, Gafencu AV. Apolipoprotein C1: its pleiotropic effects in lipid metabolism and beyond. *Int J Mol Sci*. 2019;20. doi:10.3390/ijms20235939.
43. Kulminski AM, Loika Y, Culminskaya I, et al.; Long Life Family Study Research Group. Independent associations of TOMM40 and APOE variants with body mass index. *Aging Cell*. 2019;18:e12869. doi:10.1111/acel.12869
44. Kulminski AM, Raghavachari N, Arbeev KG, et al. Protective role of the apolipoprotein E2 allele in age-related disease traits and survival: evidence from the Long Life Family Study. *Biogerontology*. 2016;17:893–905. doi:10.1007/s10522-016-9659-3