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Commentary

Evolutionary Selection of *APOE* ε4 Encourages Increased Focus on Immunity in Alzheimer's Disease

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Abstract. Smith and Ashford present a compelling hypothesis on evolution of *APOE* alleles, namely that ε4 prevalence is mediated by immune selection pressure against enteric pathogens. While the ε3 allele is more prevalent today, it outcompeted ε4 only relatively recently, as immune selection pressure for more effective immune responses to such pathogens was alleviated with transition to agrarian from hunter-gatherer lifestyles. Smith and Ashford's hypothesis is intriguing in itself, but the implications for *APOE* ε4 function in Alzheimer's disease are even more so and encourage greater focus on specific aspects of immunity in accounting for both ε4-mediated and general Alzheimer's disease risk.

Keywords: Alzheimer's disease, *APOE*, immunity, pathogen, selection pressure

A major issue with respect to Alzheimer's disease (AD) is that *APOE* ε4 (ε4) substantially increases disease risk relative to other *APOE* alleles (ε3 and ε2), in a dose-dependent manner: ε4 heterozygotes have about three times greater risk than those with the most prominent ε3 allele, while ε4 homozygotes have about 8–12 fold greater risk [1]. The ε4 allele is also reported to preferentially impact AD risk in females, and is associated with both increased amyloid deposits and younger age of onset, at least until more advanced ages [2]. Despite these clear impacts on AD risk and features, the pleiotropic function of *APOE* has made it difficult to discern exactly how it impacts AD risk. Our current understanding of *APOE* function is that its predominant physiological role is in cholesterol clearance and lipid metabolism [3]. Nevertheless, ε4 in particular has been implicated in differential amyloid processing, synaptogenesis and neuronal signaling, age-related memory retention, cognition, glucose dysregulation, and innate immune functions, among others [2–5]. Nevertheless, how any of these primary or tangential functions impact the onset, progression, or severity of AD remains incompletely understood.

What Smith and Ashford [6] suggest is that the prevalence of *APOE* alleles has been recently driven by immune selection pressure. To be clear, selective pressures on gene variants do not necessarily impact the primary function of their protein products, but they can help clarify how tangential functions can impact disease risk. A parallel example of this is in sickle cell trait, in which a mutation in the β-hemoglobin gene elicits protection against malaria

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in heterozygotes, paired with sickle cell disease in the less prevalent homozygotes, in a classical example of balancing selection. The overall impact is a net increase in reproductive fitness, fixing the mutation at a relatively high frequency (up to 18%) in populations with high malaria incidence [7]. It does this by affecting hemoglobin levels and red blood cell survival rather than modulating the primary oxygen-carrying function of the protein directly. Moreover, the allele frequency in affected populations suggests that partial protection from disease can result in relatively high retention, even with deleterious variants. Similarly, disease selection pressure on *APOE* alleles may not tell us so much about how its primary function in lipid metabolism impacts AD but may offer insight into how one of its more tangential functions does. In essence, a selection pressure driving risk-associated *APOE* allele retention for one class of diseases, might perhaps give us an idea of how *APOE* ε4 influences the risk of another in AD. In addition, it could potentially account for a degree of the difference in ε3 and ε4 prevalence.

More specifically, Smith and Ashford [6] suggest that recent evolution of *APOE* allele prevalence is driven by relaxed pressure to maintain the most effective immune responses against gut pathogens. In this context, ε4 appears both to be the ancestral allele until about 200,000 years ago and is today retained at a much higher frequency in populations subjected to higher levels of enteric pathogen infection. These modern populations typically exhibit elevated innate immunity and more effective immune responses to enteric pathogens, as well as better pathogen clearance and lower disease severity. Smith and Ashford [6] point to evidence of elevated innate immune responses in ε4 carriers: type I cytokine production in response to inflammatory stimuli, increased effector activity in glial cells, and related phenomena. They also highlight decreased gut pathogen burden in ε4 carriers, which may involve immune processes beyond solely innate and/or glial cell responses. Thus, the complexity of gut pathogen immune clearance and how it may be impacted by ε4 still requires considerable unravelling. Nevertheless, the usefulness of Smith & Ashford's hypothesis [6] is that it encourages more focused inquiry into whether and how immune activity contributes to the impact of ε4 on AD risk.

What might such inquiry look like? Whether immune modulation contributes to ε4's impact on AD could be tested by examining effects of ε4 that are reproducible in cells and/or animals (amyloid production/aggregation, lipid metabolism, AD pathology and progression, etc.), in the presence or absence of responding innate and/or adaptive immune cells. Differences in these parameters could then be monitored between $\varepsilon4^+$ and $\varepsilon4^-$ cells and/or hosts. On the clinical side, the impact of ε4 on age of onset, female bias, amyloidosis, cognitive impairment, or other known effects, could be compared in patients with low and high levels of specific innate and adaptive immune components or effectors, or with and without (or before and after) immune-modulating treatments for independent conditions.

The effect of ε4 on AD risk also varies by ethnicity, various environmental exposures, and additional variation at the *APOE* gene locus [8–10]. Such points need specific consideration if expanding Smith & Ashford's hypothesis [6] to AD. Nevertheless, the idea that ε4's impact on AD is related to immune function is corroborated by two large studies, in which systemic inflammation in ε4 carriers was associated with onset of AD and biomarkers of neurodegeneration [11, 12]. Knowledge of such associations, if experimentally verified, could be of considerable value in the clinical management of cognitive risk via inflammatory and immune interventions in elderly ε4 carriers.

Of course, whether stronger immune responses to pathogens contribute to AD risk can also be examined independent of *APOE* alleles per se. In this context, it should be mentioned that innate immune activity in AD has been extensively studied, but its impact is far from clear cut: different subtypes of brain-resident innate immune (glial) cells exist in the AD brain, where they can elicit somewhat opposing effects on the disease. Moreover, neuroinflammation, the process mediated by glial cells, has been examined epidemiologically and targeted therapeutically with mixed results: while epidemiological studies have repeatedly validated a role for non-steroidal anti-inflammatory drugs in reducing AD risk, such drugs have thus far failed to provide evidence of treatment benefits. Examination of *APOE* alleles has already been included in many analyses of innate immune function in AD but has offered little beyond a somewhat blurry association between ε4 and enhanced innate immune and/or glial cell function. With Smith & Ashford's [6] tantalizing linkage of pathogen protection and clearance to ε4 retention, it may be prudent to look more closely at adaptive immune features that cross-communicate with innate immunity, but additionally confer unique properties in the resolution of pathogen infections. Far less is known about these adaptive cells' roles in AD (i.e., B and espe-

cially T cells), but this is attracting more attention from researchers. Smith & Ashford's hypothesis [6] highlights that such responses generally, and those mediated by tissue-resident immune cells in the gut in particular, deserve at least as much scrutiny as localized innate immune activity in AD, and look forward to more studies on them that incorporate monitoring *APOE* allele-specific cross-talk in particular.

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CONFLICT OF INTEREST

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