Imaging and rare *APOE* alleles

Alzheimer disease as a developmental disorder

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The association between genetic variants in *APOE* and risk of Alzheimer disease (AD) is well known and there exists a considerable body of research into how the 3 major isoforms of *APOE*-encoded ApoE (ε2, ε3, and ε4) contribute to AD pathology.[1] These investigations have largely focused on how these different isoforms differentially modulate β-amyloid aggregation and clearance, but a growing body of research suggests these alleles also have important developmental effects that may set up a neuroanatomical vulnerability to AD. Shaw et al.[2] were the first to demonstrate that ε4 carriers exhibited cortical thinning and reduced volumes in AD-vulnerable brain regions during adolescence. Several years later, Knickmeyer et al.[3] demonstrated that this effect was already present at birth, suggesting an origin in prenatal brain development. Complementary work in mice expressing human ApoE isoforms indicated that the ε4 allele reduces dendritic spine density as early as 1 month of age (approximately equivalent to a prepubertal child). The ε2 allele resulted in longer dendritic spines and increased complexity at 1 month of age.[4] In addition, several studies have reported better cognitive performance in young ε4 carriers, indicating possible pleiotropic effects on cognition across the lifespan, such that ε4-related benefits in childhood reverse to become risk factors for cognitive impairment and dementia in later life.[5] However, a 2012 meta-analysis found no beneficial results of the ε4 allele on cognition in children, adolescents, and young adults.[6]

In this issue of *Neurology*®, Chang et al.[7] substantially extend this literature by examining how *APOE* allele status influences brain structure and cognitive performance using a large and well-characterized sample (n = 1,187; approximately half female) ranging from 3 to 20 years of age. Neuroimaging outcomes include subcortical volumes and fractional anisotropy (an index of myelination and microstructural integrity), and cortical volumes, thickness, and surface area in 20 regions of interest, selected for their relevance to AD. Also assessed were measures of cognitive flexibility, visual attention, episodic memory, and working memory selected from the NIH Toolbox Cognition Battery. This impressive collaborative effort among 10 different sites participating in the PING (Pediatric Imaging, Neurocognition, and Genetics) Consortium has allowed the authors to examine all 6 allele permutations (ε2ε2, ε2ε3, ε3ε3, ε3ε4, ε4ε4, and ε2ε4) including rare allelic groups that have either been excluded from previous research or collapsed into broader categories. Admirable efforts were made to control for covariates, including genetic ancestry, socioeconomic status, and variation in scanner devices among different sites, in addition to sex and age. Major findings include widespread and relatively stable reductions in cortical surface area in ε2ε4 children, altered age-related slopes for cortical volume and thickness in ε2ε4 and ε4ε4 children, smaller hippocampal volumes in younger ε2ε4 children and lower hippocampal fractional anisotropy in younger ε4ε4 children, which mirror findings in elderly ε4 and ε2 carriers,[8] and poorer performance on attention and working memory tasks in younger ε2ε4 and ε4ε4 children. Taken together, these results argue against an early, beneficial effect of the ε4 allele for either cognitive performance or brain development.

The major strength of the reported study is the large sample size and the breadth of neuroimaging and cognitive measures collected. The major limitation is its reliance on cross-sectional data to interpret genetic effects on neurodevelopmental trajectories. Brain development is a highly dynamic process with substantial interindividual variation. Hence, inferential errors can result from even superb cross-sectional research. This is particularly problematic when sample sizes are relatively small. Here, the rare allelic groups comprise approximately 25 to 28 cases for ε4ε4 and 17 to 19 cases for ε2ε4, depending on the phenotype examined. Given the wide age range of the study (17 years), each age point is represented by only a few individuals of the ε4ε4, ε2ε4, and ε2ε2 cases relative to the larger number (140–730) of more common *APOE* genotypes. For this reason, the most rare, ε2ε2, cases were not included in group analyses. Despite these caveats, the results are extremely

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intriguing and should stimulate additional research in large, longitudinal samples to confirm the true developmental trajectories of ε4ε4, ε2ε4, and ε2ε2 children. It is also clear from the data presented that collapsing rare allelic groups into broader categories for research is inadvisable, as brain development, aging, and cognition may vary substantially across specific ε4 or ε2 genotypes.

While these results do not have immediate implications for the clinic, they confirm that ApoE affects brain morphometry and function early in life in ways that are independent from β-amyloid, and support the provocative idea that AD is, in part, a developmental disorder. This perspective is likely germane to a number of neuropsychiatric disorders and should push investigators to look ever earlier, to the initiation of relevant neurodevelopmental processes and what might tip the balance away from disease toward healthier outcomes. Ultimately, studying *APOE* polymorphisms in young children may allow us to develop behavioral interventions and pharmaceutical agents that could normalize adverse developmental trajectories, thereby postponing the onset of AD or reducing its severity.

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