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Longevity and cognitive resilience in a Colombian family carrying the *APOE* ϵ2 variant

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Abstract

APOE is the strongest genetic risk factor for late-onset Alzheimer's disease. Despite global efforts to promote resilience, delay cognitive decline, and slow aging, *APOE* ϵ2, one of the most robust resilience-associated variants, remains relatively underexplored in translational research. Exceptional longevity offers a window into cognitive trajectories. We present clinical, cognitive and neuroimaging data from five *APOE* ϵ2/ϵ3 siblings aged 94–105. Cognition ranged from normal to mild dementia. MRI showed less atrophy than expected for advanced age, and FDG-PET revealed preserved metabolism. Findings demonstrate *APOE* ϵ2-associated resilience in the oldest-old and offer insight into mechanisms of exceptional cognitive aging with potential translational relevance.

Keywords

Alzheimer's disease, *APOE*2, Apolipoprotein E, centenarians, cognitive resilience, longevity

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Introduction

Global aging increases the prevalence of age-related comorbidities and neurodegenerative diseases, including Alzheimer's disease (AD).[1] Among the genetic contributors to late-onset AD, the Apolipoprotein E (*APOE*) ϵ4 allele represents the most significant risk factor.[2,3] In contrast, the ϵ2 variant (*APOE* ϵ2) has been consistently associated with reduced AD risk and greater longevity.[4–7] In this context, preserved cognition may reflect resistance (limited neuropathology and downstream neurodegeneration) or resilience (maintained function despite pathology), the latter being more common in the oldest-old.[8]

Inconsistent associations between *APOE* ϵ2 and both longevity and healthy aging, likely due to cohort differences, rare genotype frequencies (ϵ2/ϵ2), or variable phenotyping of aging outcomes,[9] suggests that *APOE* ϵ2-associated resilience depends on interacting biological pathways rather than genotype alone. There is substantial scientific interest in developing interventions that promote resilience, slow cognitive decline, and extend healthy lifespan.[6,10] Experimental models targeting *APOE* ϵ2-mediated pathways remain largely preclinical but have identified potential mechanisms that may inform future strategies to promote

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cognitive resilience and healthy aging.[6,10,11] Yet, few translational efforts have focused on using *APOE* ϵ2-mediated biology as a therapeutic or geroprotective strategy, including modulation of *APOE* pathways[10] or *APOE* ϵ2 gene delivery,[11] despite its status as one of the most compelling human examples of resilience-associated genetics.[12–14]

This study examines five Colombian siblings (all *APOE* ϵ2/ϵ3 carriers), aged 90 + to explore factors contributing to exceptional longevity and age-related changes. We present available medical, cognitive, and neuroimaging data, including magnetic resonance imaging (MRI) and ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET).

Methods

Participants

From a family of fourteen siblings, we evaluated five living *APOE* ϵ2/ϵ3 heterozygous siblings (two males, aged 94 and 96; three females, including 97-year-old dizygotic twins and a 104-year-old), all raised in the same region (Figure 1). Two long-lived siblings died after age 80 (at 86 from chronic obstructive pulmonary disease complications and at 97 from an unknown cause). Data for the remaining siblings was unavailable.

Study design

Non-institutionalized participants underwent Spanish-language home assessments. Four participants received baseline and one-year follow-up medical and neuropsychological evaluations. Due to geographic constraints, the fifth participant (Case 4) missed baseline neuropsychological testing but completed all follow-up assessments. Lipid profiles (total cholesterol, LDL-C, HDL-C, triglycerides, VLDL-C) were collected at follow-up (Supplemental Table 1).

Neuroimaging

Four participants underwent 3-Tesla MRI (Tim Trio, Siemens; analyzed via FreeSurfer v7.2) and FDG-PET for glucose metabolism[15–17] at Hospital Pablo Tobón Uribe (Medellín, Colombia). FDG-PET images were normalized to Montreal Neurological Institute (MNI) standard space, smoothed (8-mm^3 Gaussian filter), and converted to standardized uptake value ratios (SUVRs), using the cerebellum as the reference region. Specialists (neuroradiologist, nuclear medicine physician) provided clinical readings.

Cognitive measures

Neuropsychological assessments included the Mini-Mental State Examination (MMSE) and the Consortium to Establish a Registry for Alzheimer's Disease Word List Learning Test (CERAD-WLL), including its delayed free recall and recognition components.[18,19] Functional staging was determined using the Functional Assessment Staging Tool (FAST)[18,19] (scores 1–2: unimpaired cognition; 3: mild cognitive impairment (MCI); ≥4: dementia. Testing was optimized to minimize the impact of sensory limitations, reporting only reliably administered results.

Clinical classification followed the National Institute on Aging and the Alzheimer's Association (NIA-AA) Workgroup criteria for MCI due to AD and for dementia due to AD[20,21] (Supplemental Material).

Genotyping

Genotyping was performed using polymerase chain reaction (PCR) amplification and Sanger sequencing, complemented by whole-genome sequencing (WGS)[22–24] (Supplemental Material).

Results

Case 1: Female, 104 years, 6 years of education. At baseline, she presented significant visual and hearing impairment, without other comorbidities. She reported subjective memory concerns without functional decline, required supervision for some daily activities due to sensory deficits. She showed reduced delayed free-recall but preserved recognition on the CERAD-WLL and preserved global cognition (FAST=2; MMSE=25). At age 105, she reported additional memory difficulties and occasional temporal disorientation, requiring greater effort for instrumental activities but maintaining independence. A mild global cognitive decline was observed, while CERAD-WLL performance remained stable (Table 1), consistent with MCI (FAST=3; MMSE=22). Lipids showed borderline elevated total cholesterol and LDL-C levels. Neuroimaging, performed only at baseline, showed moderate-to-severe atrophy, most prominent in the right parietal lobe, with mild microangiopathic changes. FDG-PET showed relative higher precuneal/frontal metabolism compared to younger siblings.

Case 2: Female, 97 years, 7 years of education, dizygotic twin to case 3. At baseline, presented with marked visual impairment and mobility-limiting meniscopathy, unmedicated dyslipidemia, hypothyroidism, and chronic lung disease of unspecified etiology. She did not have polypharmacy (Supplemental Table 1). Family members reported prominent memory difficulties. She had mild functional impact and low global cognitive performance, particularly in delayed free-recall and recognition, consistent with mild dementia (FAST=4; MMSE=19). At age 98, cognition remained stable (Table 1) (FAST=4; MMSE=18). Lipids showed elevated total cholesterol and LDL-C levels. Baseline MRI showed mild temporal and right-predominant insular atrophy, mild global atrophy less pronounced than expected for her age, and mild microangiopathy. Follow-up MRI showed no significant

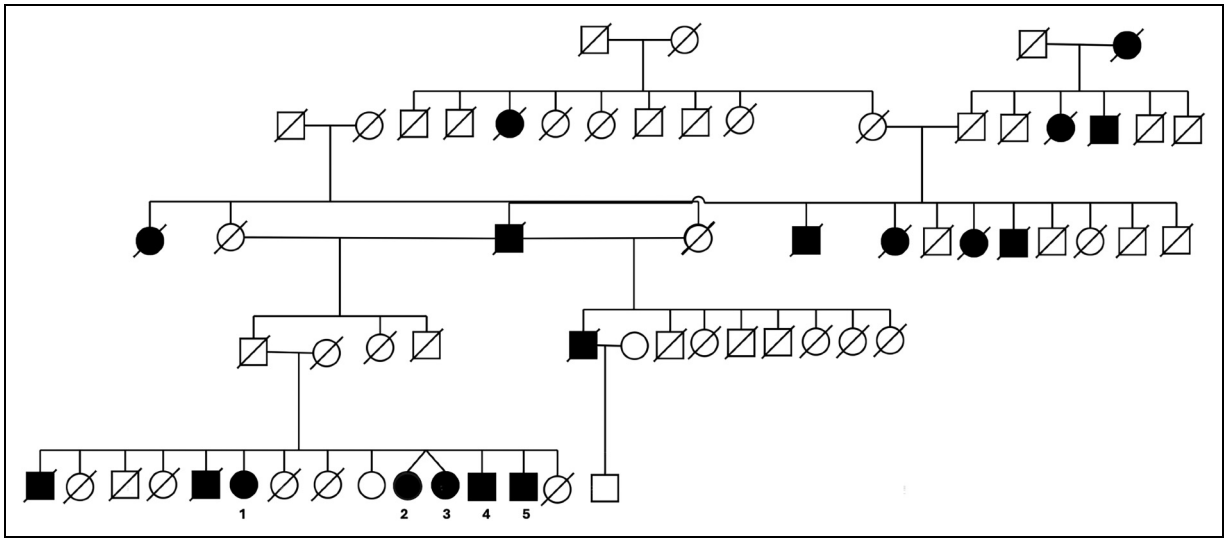


Figure 1. Genealogy of the family. Dark-filled symbols indicate members who exceeded 70 years of age at the moment of death or the moment of the last visit. Circles represent females, squares represent males. Deceased individuals are marked with a crossed bar. Numbered individuals correspond to the case identifiers described in the manuscript.

Table 1. Sociodemographic and cognitive characterization of the patients.

Case		Case 1	Case 2	Case 3	Case 4	Case 5
Sex		Female	Female	Female	Male	Male
Age (years)		104	97	97	96	94
Education (years)		6	7	7	8	11
Visit 1	MMSE /30	25	19	21	N/A	24
	WLL-Delayed Free Recall/10	1	0	2	N/A	1
	WLL-Recognition/10	8	2	7	N/A	5
	FAST /7	2	4	3	N/A	1
Visit 2	MMSE /30	22	18	20	19	25
	WLL-Delayed Free Recall/10	1	0	1	0	3
	WLL-Recognition/10	8	5	8	5	7
	FAST /7	3	4	3	3	2

MMSE: Mini-Mental Status Examination; CERAD-WLL: Consortium to Establish a Registry for Alzheimer's Disease Test Battery- Word List Learning test; FAST: Functional Assessment Staging Tool.
N/A: Not applicable, as the participant did not undergo neuropsychological evaluation during visit 1.

progression, with only slight hippocampal atrophy. Baseline and follow-up FDG-PET demonstrated preserved age-adjusted glucose metabolism.

Case 3: Female, 97 years, 7 years of education, dizygotic twin to Case 2. At baseline, presented with dyslipidemia, hypertension, hypothyroidism, migraine, diabetes, obstructive sleep apnea, and arthrosis. She was taking rosuvastatin 40 mg daily and had polypharmacy (Supplemental Table 1). Marked hearing loss limited cognitive assessment. At age 97, she and her family reported memory-related difficulties, mild functional limitations attributed to her comorbidities rather than cognitive decline. Her delayed free-recall scores were low, while recognition remained preserved. She met criteria for MCI (FAST=3; MMSE=21). At age 98, clinical status remained largely stable (FAST=3; MMSE=20). Lipids showed mildly elevated broad-spectrum cholesterol levels. Neuroimaging, performed only at baseline, revealed age-related atrophy, less pronounced than her twin's, with mild frontoparietal atrophy, relative hippocampal preservation, and mild microangiopathy. FDG-PET demonstrated preserved age-adjusted glucose metabolism.

Case 4: Male, 96 years, 8 years of education. Professionally active (farming) until age 86. History included hearing loss, hypertension, coronary artery disease, osteoarthritis, and a prior COVID-19 infection. He was taking atorvastatin 20 mg nightly and did not have polypharmacy (Supplemental Table 1). At baseline, he underwent only a medical evaluation and reported mild post-COVID memory complaints without functional impact. At age 97,

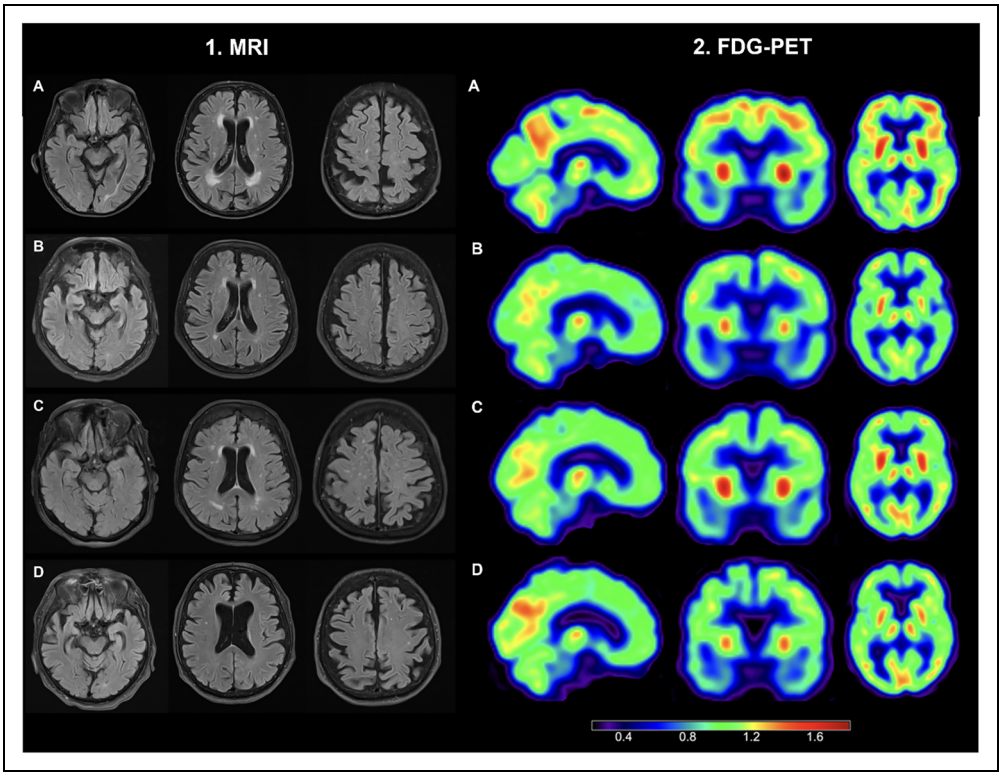


Figure 2. Brain MRI and FDG-PET scans of the APOEε2 heterozygous cases. Panel 1. Fluid-Limited Angle Inversion Recovery (FLAIR) MRI Scans of the Brain, corresponding to the most recent imaging available: baseline scans for Cases 1 and 3, and follow-up scans for Cases 2 and 5. Axial slices are presented showing cerebral anatomy at different levels in cases with available neuroimaging, illustrating individual patterns of cerebral atrophy and white matter disease. The rows correspond to: A. Case 1 (104F); B. Case 2 (98F); C. Case 3 (97F); and D. Case 5 (95M). Panel 2. FDG-PET scans assessing cerebral glucose metabolism using FDG-PET SUVR at baseline. Lower SUVR (cold colors) represent lower metabolism and higher SUVR (warm colors) represent higher metabolism. FDG columns represent sagittal, coronal and axial slices. The rows correspond to: A. Case 1 (104F); B. Case 2 (97F); C. Case 3 (97F); and D. Case 5 (94M).

his memory concerns increased without impact on daily functioning. Low performance on cognitive testing was observed, characterized by low delayed free-recall scores and partially preserved recognition, consistent with MCI (FAST=3; MMSE=19). Lipids were within normal limits, and no neuroimaging studies were performed.

Case 5: Male, 94 years, 11 years of education. History of dyslipidemia, hypertension, benign prostatic hyperplasia and insomnia, all diagnosed after age 85, and a myocardial infarction at 94. He was taking atorvastatin 20 mg daily and had polypharmacy (Supplemental Table 1). At baseline, he had no cognitive complaints, remained fully independent, and showed global cognitive performance within normal limits, despite low delayed free-recall score and partially preserved recognition (FAST=1; MMSE=24). At age 95, global cognition remained within normal limits, with improved memory test performance, mild naming difficulties and subjective memory concerns (FAST=2; MMSE=25). Lipids were within normal ranges. Baseline and follow-up MRI showed symmetrical age-related diffuse atrophy, mild ventricular enlargement, preserved hippocampal volumes, and mild leukoaraiosis. FDG-PET, both at baseline and follow-up, demonstrated preserved age-adjusted glucose metabolism.

Overall clinical profiles

Across the five siblings (aged 94–105), three clinical profiles emerged (Table 1). Cases 1, 3, and 4 exhibited subjective or mild objective memory deficits, characterized by low delayed free-recall performance, preserved or partially preserved recognition and minimal or no functional impairment. Case 2 demonstrated mild dementia with functional impact, marked recall and recognition deficits, and stable cognitive performance over the one year follow up. Case 5 showed largely preserved cognition, apart from low delayed free-recall scores, and maintained full independence despite advanced age and late-onset vascular risk factors.

Neuroimaging (Figure 2) revealed age-related changes in all participants. Notably, atrophy was milder than expected for extreme longevity (except Case 1). Across all cases, metabolic activity on FDG-PET was preserved for age in brain regions associated with cognitive resilience.

Neuroimaging was not available for Case 4, limiting direct imaging comparison across all siblings.

Discussion

This case series of five exceptionally long-lived *APOE* ϵ2 carriers, reveals heterogeneous cognitive profiles despite shared familial, environmental, and genetic backgrounds, aligning with evidence linking *APOE* ϵ2 to reduced cognitive decline,[10,25] although its association with exceptional longevity appears more robust.[9] While family-based observational designs cannot fully disentangle the relative contributions of *APOE* ϵ2 and other shared life-course factors, the included twin pair provides valuable within-family comparisons, accounting for shared genetics, that complements the overall narrative of *APOE* ϵ2-associated resilience. Ultimately, the observed patterns likely reflect a multifactorial interplay of genetic susceptibility, shared environments, and individual lifespan variability.

A consistent finding was reduced delayed free-recall performance, even among individuals with preserved global cognition and functional independence, suggesting that this measure may have limited sensitivity in the oldest-old. In contrast, recognition memory more closely reflected overall cognitive status. Thus, poor delayed free-recall performance at advanced ages may represent normative age-related patterns rather than evidence of underlying neurodegenerative processes, underscoring the need to revisit the relevance of normative data tailored to exceptional longevity, as existing norms may not adequately reflect performance expectations in this population.[26,27]

Prevalent sensory impairments in the oldest-old severely confound cognitive assessments, highlighting a critical need for sensory-adapted diagnostic tools, as observed in Cases 1–3. Visual and auditory deficits can limit test administration, reduce reliability and influence observed test scores.[26] This underscores the methodological challenge posed by the lack of cognitively appropriate assessment tools adapted to minimize sensory demands, which is essential for accurate interpretation of cognitive performance in exceptionally long-lived adults.[28] Psychomotor slowing, reduced processing speed, polypharmacy, and fatigue may resemble or amplify cognitive deficits, making it difficult to distinguish normal age-related changes from true impairment.[26,29–31]

Functional assessment also presents challenges in this age group. Family members often provide assistance with instrumental daily activities as a preventive measure, to reduce the risk of adverse events, regardless of cognitive ability. As observed in Cases 1, 2, and 3, such support can obscure true functional capacity and complicate differentiation between limitations due to physical/sensory factors from those due to cognitive decline. This underscores the need for longevity-tailored tools to prevent underestimating independence.[29,32]

Furthermore, neuroimaging highlights the dissociation that can occur between structural or metabolic changes and clinical presentation in advanced age, as preserved glucose metabolism in vulnerable regions is a proxy for neuronal integrity and functional activity.[33] Despite expected age-related MRI changes,[34,35] atrophy was unexpectedly mild (except Case 1) and FDG-PET consistently demonstrated preserved glucose metabolism—indicating neuronal integrity[33]—across all imaged cases.

Although Case 1 exhibited moderate-to-severe age-related atrophy on MRI, glucose metabolism remained preserved, with higher neuronal activity in the precuneus and frontal regions compared to younger siblings. Cognitive performance and independence were largely maintained, reflecting cognitive resilience despite structural decline.[8] Cases 2–5 showed relatively preserved brain structure and metabolism, even with variability in clinical presentation, and follow-up suggested stable cognitive and functional outcomes. Overall, these cases support the possibility of *APOE* ϵ2-associated neuroprotection in individuals with exceptional longevity.

Overall, these findings suggest that *APOE* ϵ2-associated longevity may involve reduced neurodegeneration, helping mitigate age-related cognitive decline, aligning with previous evidence.[10,14,33] The heterogeneity seen across cases highlights that additional genetic, environmental, and lifestyle factors likely contribute to resilience or vulnerability.[36] WGS ruled out other established resilience variants in this population (e.g., *APOE* Christchurch, Reelin-COLBOS).

Unlike population-level studies, this report examines a single family of five exceptionally long-lived *APOE* ϵ2/ϵ3 siblings. This rare co-occurrence of a resilience-associated allele is accompanied by concordant protective phenotypes. Although *APOE* ϵ2 inheritance is non-deterministic, its co-segregation with preserved brain structure, metabolic function, and relative cognitive stability provides biological coherence that is difficult to infer from heterogeneous cohorts. *APOE* ϵ2-associated profile observed in this family supports a relationship with both extended lifespan and cognitive resilience. Because resilience is subtle, multifactorial, and often under-recognized, this family offers a unique window into *APOE* ϵ2-mediated mechanisms contributing to exceptional aging. We hope this current study encourages the pursuit of translational approaches that leverage *APOE* ϵ2 to support longevity and healthy aging, as it highlights *APOE* ϵ2-related protective mechanisms such as preserved metabolism, informs biomarkers of resilience, and enables more precise trial design through *APOE*-based participant stratification.

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Ethical considerations

The study was approved by the institutional review board of the Research Ethics Committee at the University of Antioquia, Colombia (Code: BB-Ci-001), with the latest version of the informed consent (V5) approved on June 12, 2025. Written informed consent was obtained before any intervention and data collection. Participants were part of the Resist Alzheimer's Project at the Grupo de Neurociencias de Antioquia.

Consent to participate

Written informed consent was obtained before any intervention and data collection.

Consent for publication

Not applicable

Author contribution(s)

Alejandro Guerrero: Data curation; Formal analysis; Investigation; Methodology; Visualization; Writing – original draft; Writing – review & editing.
Nelson David Galvis-Garrido: Formal analysis; Methodology; Writing – original draft; Writing - review & editing.
Yamile Bocanegra: Data curation; Formal analysis; Investigation; Methodology; Validation; Writing – review & editing.
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Declaration of conflicting interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Quiroz and Lopera have served as consultants for Biogen. Lopera, Arboleda-Velasquez and Quiroz are co-inventors on a patent application concerning the use of *APOE*

Christchurch-related therapeutics. Arboleda-Velasquez is also a co-founder of Epoch Biotech, a company focused on developing therapies inspired by protected cases. Aguillon has served on the advisory board for Eli Lilly. All other co-authors have no conflicting interests to disclose.

Data availability statement

The data supporting the findings of this study are available on request from the corresponding author. The data is not publicly available due to privacy or ethical restrictions.

Supplemental material

Supplemental material for this article is available online.

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