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LETTER TO THE EDITOR

Population diversity validation for Alzheimer's disease "unifying" models

Coleman and colleagues[1] have made exceptional contributions by proposing stress granule formation and nucleocytoplasmic transport disruption as a unifying mechanism linking Alzheimer's disease (AD) risk factors to massive gene expression changes.[1] Their framework elegantly integrates previously disparate findings—from amyloid beta and tau pathology to inflammation, synaptic dysfunction, and cell death—into a testable model with clear therapeutic implications. The evidence supporting each component is substantial, and the model's potential to guide biomarker development and early intervention is significant.

However, responsible clinical translation requires examining whether this "unifying principle" applies universally or reflects patterns specific to studied populations. This concern is not unique to Coleman et al.—it represents a field-wide challenge where major neuroimaging and genomic studies systematically underrepresent 85%–95% of global population diversity.[2] When demographic homogeneity characterizes foundational research, resulting frameworks face fundamental validity threats regardless of technical excellence.

1 | BIOLOGICAL MECHANISMS SUGGEST POPULATION-LEVEL VARIATION

Multiple components of Coleman's model show documented population-level variation. Nucleoporin genes (*NUP62*, *NUP98*, and *NUP153*, among others central to their model) demonstrate significant allele frequency differences across populations.[3] Stress response pathways, including eIF2α phosphorylation that triggers stress granule assembly, show genetic variants with population stratification.[4] Epigenetic modifications—which Coleman identifies as critical to gene expression changes—vary substantially based on environmental exposures that differ systematically across populations experiencing different social determinants of health.[5]

Coleman and colleagues[1] appropriately notes that the apolipoprotein E (*APOE*) ε4 allele affects stress granule formation but does not acknowledge that the effects of *APOE* ε4' on Alzheimer's disease (AD) risk and pathology vary significantly by ancestry.[6] If one key genetic risk factor shows population-specific effects, other components of the proposed mechanism likely do as well. Environmental risk factors highlighted by Coleman (pesticides, metals, and air pollution) have highly variable exposure patterns globally, potentially creating different baselines for cellular stress responses and stress granule formation.

1.1 | Evidence from diagnostic algorithm development

Experience with other neurological diagnostic frameworks demonstrates that demographic homogeneity in development cohorts predicts performance disparities in diverse populations. Brain age prediction models—using analytical approaches similar to those Coleman proposes for biomarker development—show systematic errors when applied across populations not represented in training data.[7] Alzheimer's screening algorithms exhibit doubled false-positive rates in underrepresented populations.[8] When baseline biological parameters differ across populations, diagnostic cutoffs optimized for one group may systematically misclassify others.

Coleman's model proposes stress granule markers and nucleocytoplasmic transport measures as "early biomarkers that precede those currently used." If baseline stress granule formation rates, nucleoporin expression levels, or epigenetic patterns vary across populations due to genetic or environmental factors, biomarker thresholds established in demographically homogeneous cohorts may produce population-specific false positives or false negatives.

1.2 | Constructive pathways for validation

Several actionable approaches could establish whether Coleman's framework represents universal AD biology or requires population-specific calibration:

1. **Multi-ancestry genetic studies**: Examine whether nucleoporin variants, stress response genes, and epigenetic modifiers associated with AD show consistent effects across populations or population-specific patterns.
2. **Environmental stratification**: Test whether differential exposure to risk factors (air pollution, pesticides, metals) correlates with stress

granule markers and gene expression patterns within and across populations.

3. **Cross-population biomarker validation**: Before clinical deployment, validate proposed stress granule and nucleocytoplasmic transport biomarkers in diverse cohorts, establishing population-specific normative data, if needed.
4. **International collaboration**: Partner with research groups in Africa, Latin America, Asia, and underrepresented populations in Western countries to determine whether the model's predictions hold universally.

The paper's observation that "different neurodegenerative diseases show both common and disparate alterations" should prompt the parallel question: Do different populations show disparate patterns even within AD? Coleman demonstrates that single neurons in the same brain show variable stress granule formation and disease progression—acknowledging within-individual diversity. Extending this recognition to between-population diversity represents scientific rigor rather than methodological burden.

2 | CONCLUSION

Coleman et al. have provided an outstanding foundation for understanding AD pathobiology. International collaborations building on this work could establish whether stress granule formation and nucleocytoplasmic transport disruption represent universal mechanisms or show population-specific patterns requiring adapted diagnostic and therapeutic approaches. A truly unifying model must ultimately account for the full spectrum of human neurological diversity.[9,10] This represents opportunity rather than limitation—realizing this work's full clinical potential for the 55 million people living with dementia worldwide.

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CONFLICT OF INTEREST STATEMENT

The author has no conflict of interest pertaining to the content of this manuscript. Author disclosures are available in the supporting information.

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