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The Genetic Basis of Alzheimer's Disease: Phenotype-Genotype Relationship in Autosomal-Dominant Alzheimer's Disease

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Autosomal Dominant Alzheimer's Disease (ADAD), the rarest form of Alzheimer's disease (AD), leads to early onset dementia and is due to a mutation within Amyloid Precursor Protein (APP), Presenilin-1 (PSEN-1), or Presenilin-2 (PSEN-2) genes. Each mutation alters the metabolism of β-amyloid (Aβ)—the protein considered to be a driving force in the physiopathogenic cascade of AD—and guarantees AD development. Like the more common, sporadic form of AD, abnormalities observed in ADAD are cerebral microbleeds (CMBs) and severe white matter hyperintensity (WMH), which are detected with imaging tools. The aim here is to evaluate these two features and their relationship with ADAD genotypes.

The Dominantly Inherited Alzheimer Network (DIAN) enrolls participants at risk for ADAD, and performs clinical, cognitive, imaging, and biochemical assessments. The symptom onset in ADAD is approximated by the afflicted parent's age of disease onset, and is termed estimated years to onset (EYO). CMBs and WMH can be observed even before symptom onset, and are indications of vascular abnormalities. Studies have shown that AD individuals with severe WMH have more CMBs.

Among ADAD mutations, the expression of the imaging biomarkers is variable. The PSEN-1 mutation is the most common mutation and has exhibited severe AD pathology. Using the DIAN data, I will correlate the participants' WMH volumes with CMBs counts, using factors such as EYO, cognitive impairment and the mutation type. I hypothesize that PSEN-1 carriers have more severe WMH and CMBs when compared to the other two mutations. I aim to further establish the trend outlined by previous studies. Further understanding ADAD pathology will increase our ability to devise therapies to control and combat AD as a whole.