Sex and Genotype Driven Disparities in Vascular Integrity, Metabolic Profile, Gut Microbiome, and Behavior in Alzheimer's Disease

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The Apolipoprotein E (APOE) gene is the most influential genetic risk factor for Alzheimer’s Disease (AD). In addition to genotype, the implication of gender must also be investigated; women have a significantly higher risk of developing AD. However, the mechanisms responsible for this phenomenon is unclear. This project utilized control data sets from previous studies and was analyzed with both t-tests and False Discovery Rate tests using GraphPad Prism. The vascular integrity was measured through MRI of the hippocampal Cerebral Blood Flow (CBF) and the behavior was measured using Radial Arm Water Mazes (RAWM) to measure both learning and recall ability. Metabolic profile was determined through tissue samples analyzed at Metabolon and the gut microbiome was determined through fecal samples analyzed at BaseSpace. In the metabolic profile, the sex drove disparities in pantothenate (p=0.000066, q=0.034) and ureidoprionate (p=0.00019, q=0.0492). The APOE genotype drove disparities in N6-methyllysine (p=<0.000001, q=<0.000001), N-acetylarginine (p=0.000061, q=0.0165), 3-ureidopropionate (p=0.000207, q=0.0373), homocarnosine(p=0.000286,q=0.0387), and N-acetylhistidine (p=0.000374, q=0.0405). In the gut microbiome, the disparities in the genera proteus and bilophila were driven by APOE alleles. In both CBF and RAWM, APOE4 female mice had the worst performance compared to both males and APOE3 mice. Each of these elements plays a significant role in the pathway of AD and understanding the fundamental mechanisms allows individualized treatment through precision therapies to become a reality.