stress may influence human AD. This analysis illustrates an important step towards translation of the results of experimental AD studies to human applications.

SYSTEMIC BIOENERGETIC CAPACITY CHANGES WITH COGNITIVE STATUS AND INSULIN SENSITIVITY IN OLDER ADULTS

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Systemic mitochondrial dysfunction is reported with AD progression, suggesting that peripheral blood cells may be used to investigate systemic mitochondrial alterations related to cognitive decline. We aimed to identify bioenergetic signatures associated with AD-related dementia and differences in insulin sensitivity associated with AD risk. We analyzed mitochondrial bioenergetics in peripheral blood cells collected from 365 older adults with varying cognitive status (normal, mild cognitive impairment, and AD) and insulin sensitivity. Normoglycemic individuals exhibited lower maximal bioenergetic capacity with AD (PBMCs: 239.6 pmol·min–1, p = 0.02; Platelets: 151.7 pmol·min–1, p = 0.06) compared to normal cognition (PBMCs: 271.5 pmol·min–1; Platelets: 171.7 pmol·min–1). Individuals with impaired insulin sensitivity exhibited lower maximal bioenergetic capacity in platelets with AD (171.6 pmol·min–1, p = 0.008) compared to normal cognition (210.6 pmol.min–1). Participants with impaired insulin sensitivity also exhibited unique bioenergetic profiles exemplified by overall higher levels of mitochondrial respiration, indicating that comorbidities such as diabetes can significantly influence bioenergetic capacity. We observed strong positive associations between maximal respiration in normoglycemic individuals with cognitive function, as measured by Modified Preclinical Alzheimer's Cognitive Composite (mPACC5) (p = 0.06), and fatty acid oxidation in individuals with impaired insulin sensitivity with cortical thickness (p = 0.05). This study demonstrates that circulating cells may provide a cost-effective and minimally invasive way to monitor systemic bioenergetic changes associated with AD risk, progression, and insulin sensitivity. These findings also suggest that blood-based bioenergetics are related to key features of AD development and progression and should be further developed as a potential biomarker.

THE HUMAN GENES THAT LINK MIDDLE-AGE COMORBIDITIES AND ALZHEIMER'S DISEASE

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Advancements in biomedical research have identified the genes influencing life spans, stress resistance and age-related diseases, including Alzheimer's disease. Stress resistance includes resistance to multiple forms of stress, pathogens and toxic beta-amyloid which is tightly associated with Alzheimer's disease. We have investigated 431 human genes that are associated with co-morbidities (Vahdati Nia et al, 2017; Le et al., 2020). Those genes are involved in lipid metabolism, hemostasis, hemostasis, neuroendocrine and immune functions. The genes are relevant to middle-life health. We explore a wide variety of co-morbidities that could happen in middle to late life. I will give a brief review of increased stress resistance, and genetic markers associated with co-morbidities. I will discuss how the studies may benefit to fight against COVID-19. References: 1. Vahdati Nia B, Kang C, Tran MG, Lee D, Murakami, S. (2017) Front. Genet. 8:55. doi: 10.3389/fgene.2017.00055 2. Le D, Crouch N, Villanueva A, Phong Ta, Dmitriyev R, Tunzi M, and Murakami S. (2020) Journal of Neurology and Experimental Neuroscience. 6;S1.

USING DROSOPHILA TO IDENTIFY NATURALLY-OCCURRING MODIFIERS OF ALZHEIMER'S DISEASE

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Despite significant progress in identifying risk factors for late-onset Alzheimer's Disease (LOAD), much of the variance in disease pathogenesis remains unexplained, likely due to the contribution of many genes of small effect size. Model organisms such as Drosophila Melanogaster exhibit conservation in both disease-causing genes and cellular processes implicated in Alzheimer's Disease (AD), offering a genetically tractable model that can be statistically leveraged to identify causal variants. Here, we combine a Drosophila model of AD with the Drosophila Genetic Reference Panel (DGRP), a model of natural variation consisting of over 200 fully sequenced, isogenic lines derived from a wild-caught population. Expression of two proteins closely associated with AD pathogenesis, A□42 and Tau, in the Drosophila eye results in a "rough eye" phenotype, an easily quantifiable phenotype caused by degeneration of the ommatidial array. By quantifying the degree of A□42- and Tau-mediated degeneration across 164 lines of the DGRP and using a gene-based approach to map associations, we have identified and validated a subset of naturally occurring modifiers of degeneration in Drosophila. Enrichment analysis reveals that the set of genes identified in our screen show significant enrichment for genes identified as significant or suggestive (4x10-6>p>2x10-11) in human GWAS studies. The results presented here provide proof-of-principal for an approach that combines the strengths of forward genetic screens in model organisms with the power of human GWAS studies to identify and validate potential risk factors that have been difficult to detect in human studies alone.

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Alzheimer's Disease and Other Dementias II

COLLECTION OF DATA ON PERSONS LIVING WITH DEMENTIA WHO GO MISSING: FIRST RESPONDER PERSPECTIVES

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