Age is major risk factor for AD; however, relationships between aging and AD are not well understood. Decline in physiological resilience is universal feature of human aging that may also play role in AD. Aging-related pathways (such as IGF-I/P53/mTOR-mediated) that are involved in tissue resilience work in concert to decide outcomes of cell responses to stress/damage, such as survival, apoptosis, autophagy, etc. We hypothesized that interplay among genes in these pathways may influence AD risk as result of epistasis (GxG). We estimated effects of pairwise epistasis between SNPs in 53 genes from respective pathways on AD risk in the LLFS compared with other data (HRS, CHS, LOADFS). We found significant (fdr<0.05) GxG effects on AD risk in older adults across datasets. The SNP rs11765954 in CDK6 gene was involved in top GxG effects on AD in all datasets, when paired with SNPs in BCL2 and PPARGC1A. The CDK6 role in AD could be pleiotropic, depending on its activity in neurons: CDK6 expression is needed for DNA repair and neuronal survival; however, CDK6 overexpression may lead to the cell cycle reentry in postmitotic neurons resulting in apoptosis, which may contribute to neurodegeneration. CDK6 was earlier found to interfere with BCL2 effects on apoptosis, and with PPARGC1A effects on energy metabolism, which might contribute to observed GxG between these genes. We conclude that interactions among genes from biologically connected aging pathways may significantly influence AD risk. Uncovering such GxG effects has a potential to yield new genetic targets for AD prevention/treatment.

INTERGENERATIONAL TRAUMA TRANSMISSION? TEST OF CELLULAR AGING IN MOTHERS EXPOSED TO SEXUAL ABUSE AND THEIR CHILDREN

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Exposure to maltreatment during childhood can lead to increased risk for poor health outcomes in adulthood. Child maltreatment and later poor health may be linked by premature biological aging. We tested whether childhood sexual abuse (CSA) is associated with telomere length (TL) in adult females. We further tested the hypothesis of intergenerational transmission of trauma by measuring TL in both CSA-exposed and non-exposed mothers and their children. TL was measured in a subset of participants and their children from a prospective-longitudinal cohort study of sexually abused females and a demographically matched comparison group. Linear regression models were used to test for associations between CSA-exposure and age-adjusted TL in females (N=108, mean age 36.3 years). Multilevel linear models were used to test the intergenerational effect of maternal-CSA exposure on age-adjusted TL in their children (N=124 children mean age 10.5 years across 61 mothers). CSA-exposure was not associated with TL in females. Replicating previous work in this area, maternal TL and sex were significant predictors of child TL in all models tested. Longer maternal TL predicted longer TL in children, and female children had longer TL than male children. Maternal-CSA exposure did not predict TL in children. This finding is in line with some previous results on CSA and TL measured in adulthood. Previous significant results associating child maltreatment with shorter TL in adulthood may be capturing a population of individuals exposed to either multiple types of maltreatment or maltreatment in childhood with concurrent TL measurements.

METRICS OF PHENOTYPIC AGING FROM THE ENERGETICS PERSPECTIVE

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Identifying the most critical metrics of aging is an ongoing challenge due to a lack of comprehensive measurements and heterogeneity of the aging process. Using the Baltimore Longitudinal Study of Aging, we developed a conceptual framework to identify metrics of aging that capture the hierarchical and temporal relationships between functional aging, phenotypic aging, and biological aging based on four hypothesized domains: energy regulation, body composition, homeostatic mechanisms, and neurodegeneration. Focusing on the energetics domain, we examined trajectories of eight phenotypes using more than 10 years of longitudinal data. The standardized Cronbach's alpha for these variables was 0.80, providing construct validity of our concept. We further implemented item response theory to integrate these phenotypes into a summarized energy score. Linear mixed models were used to assess the cross-sectional and longitudinal associations between the summarized energy score and physical functioning as measured by gait speed and time to walk 400m as quickly as possible (number of participants ~ 811, number of observations ~ 1700). After adjusting for age, sex, weight, and height, a higher summarized energy score was independently associated with faster baseline gait speed (0.13 m/s, p<0.001) and faster 400m time (-35.3 seconds, p<0.001), and longitudinally associated with slower gait speed decline (0.08 m/s/decade, p<0.001) and slower 400m time increase (-37.8 secs/decade, p<0.001). This work demonstrates the utility of our energetics domain-based summarized score. Moving forward, it will be important to clarify relationships between this summarized score and other functional metrics and assess its generalizability to the other cohorts.

NEUTROPHIL-LYMPHOCYTE RATIO AND MORTALITY IN THE LONG LIFE FAMILY STUDY

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