Longevity Consortium (LC) and how their cooperative research is designed to discover molecular factors and pathways that can predict healthy human aging and longevity, associate with extreme human lifespan, show relevance to chronic age-related conditions, respond to interventions to slow aging in mice, and show evidence for association with lifespan across species. A systems biology approach is undertaken to identify common molecular features across human traits and organisms, and a chemoinformatics approach to link molecular targets to candidate healthy aging interventions. The LC results are made publicly available and we provide funding opportunities to the scientific community to support pilot projects.

GENOME-WIDE ASSOCIATION STUDY OF EXTREME HUMAN LONGEVITY DISCOVERS UNCOMMON LONGEVITY VARIANTS

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The strong heritability of extreme human longevity supports the hypothesis that this is a genetically-regulated trait. However, association studies focused on common genetic variants have discovered a limited number of longevity-associated genes. We conducted a genome-wide association study of 4,216 individuals including 1317 centenarians from the New England Centenarian Study (median age = 104 years) using >9M genetic variants imputed to the HRC panel of ~65,000 haplotypes. The set included approximately 5M uncommon variants. The associations were tested using a mixed effect logistic regression model with genotype-based kinship covariance of the random effects to adjust for cryptic relations using the package GENESIS. The analysis discovered 45 genome-wide significant SNPs (p< 5E-08) including 8 new loci in chromosomes 3, 6, 7, 9, 10, 14 and 15 in addition to the APOE locus. The list includes new pQTLs in serum that suggest a new biological mechanism involved in extreme human longevity.

THE PROTEOMICS OF LONGEVITY

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The biological underpinnings of longevity are poorly elucidated in humans. We used a novel, high-throughput discovery-proteomics approach to identify serum proteins associated with longevity (living beyond 90th percentile of survival) in community-dwelling men age ≥65 years in the MrOs Study. Baseline serum from 2473 men was analyzed using liquid chromatography-ion mobility-mass spectrometry. >21,000 peptides and 2931 proteins were recognized. Twenty-five proteins significantly associated with attainment of longevity over 15 yrs of observation were identified using rigorous statistical methods. 25 proteins were significantly associated; all were lower in long lived men than in men dying earlier. Most longevity-associated proteins were from inflammatory pathways; some have multifunctional biological roles potentially reflecting other mechanisms. Pathway analyses suggest important upstream regulators may be causally responsible for the associations. These results provide the opportunity to evaluate these proteins as biomarkers, and highlight the potential importance of their biological pathways in the origins of long life.

MULTI-OMIC BIOLOGICAL AGE ESTIMATION, CORRELATION WITH WELLNESS, DISEASE PHENOTYPES: LONGITUDINAL SAMPLE OF 3558

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Biological age (BA) has been shown to be a better predictor of mortality and disease than chronological age (CA). Aging's diverse effects are visible across many data types. We investigated BA from deep phenotyping of 3558 wellness program participants and controls. The Klemera-Doubal BA estimation algorithm was applied to genetic and longitudinal clinical laboratory, metabolomic, and proteomic assay data. BA trajectories were calculated using Generalized Estimating Equations. BA of individuals with Type-2 Diabetes averaged 6+ years greater than CA. Wellness program participation decreased individuals' rate of aging (coefficient: -0.16, 95% CI: -0.45, 0.19), with effects dependent on sex, initial BA, and CA. Measures of metabolic health, inflammation, and toxin bioaccumulation were strong predictors across data types and sex. Deep phenotyping enabled calculation of a BA measure and a wellness program improved BA, either in absolute terms or relative to CA, showing it is modifiable.

GENETIC SUPPORT FOR INTERVENTIONS THOUGHT TO PROMOTE HEALTHY AGING

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We consider the human genetic targets of many proven and hypothesized pharmacologic interventions meant to promote healthy-aging and explored not only how polymorphic these targets are in the human population, but also whether these polymorphisms have been shown to impact longevity and age-related phenotypes in general. We also determined if polymorphism in the genes or proteins modulated by healthy-aging interventions have been shown to also modulate the expression levels of those genes and proteins (i.e., act as gene or protein expression quantitative trait loci – eQTLs or pQTLs, respectively) and whether they have been subjected to mediation analyses testing their potential causal relationships to aging and longevity phenotypes. We compare our results to studies of other classes of drugs used to treat specific conditions, such as hypertension.