diagnosis. Baseline CT-derived trabecular, cortical, and integral L3 BMD and DXA-derived whole body, thoracic spine, and lumbar spine BMD was highest in participants with ≥15.7% protein intake, and lowest in participants whose protein intake was <13.1% (all p<0.01). However, 5-year change in BMD was not associated with baseline dietary protein intake. Similar trends were observed in gender-stratified models and when examining intake relative to protein source (animal vs. vegetable). In summary, higher dietary protein intake was associated with greater baseline spine and whole body BMD in community-dwelling older adults.

**EFFECT OF LONG-TERM POLYPHARMACY AND THE DRUG BURDEN INDEX (DBI) ON CARDIAC FUNCTION AND FIBROSIS IN AGED MICE**

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Polypharmacy (use of ≥ 5 medications) and Drug Burden Index (DBI: measures cumulative exposure to anticholinergic and sedative drugs) impair function in older adults. Preclinical studies can provide a mechanistic understanding. We aim to evaluate the effect of chronic polypharmacy, medications with increasing DBI and deprescribing (cessation of medications) on cardiac function and histology in aged mice. Twelve-month-old male C57BL/6 mice received control feed or feeds/water containing therapeutic doses of drugs in regimens of polypharmacy with Zero DBI (simvastatin, metoprolol, omeprazole, paracetamol, ibuprofen), Low DBI (simvastatin, metoprolol, omeprazole, paracetamol, citalopram), High DBI (simvastatin, metoprolol, oxybutynin, oxycodone, citalopram) or monotherapy with each of the five drugs from the High DBI diet. At 21 months, animals were re-randomised to continue treatment or be deprescribed. Blood pressure (BP) and rotarod performance (endurance) were assessed every 3 months and hearts were collected at 27 months. Compared to control, we observed a significant decrease in systolic and diastolic BP in Zero DBI, Low DBI, metoprolol and simvastatin treated mice and not in High DBI treated mice at 21 months (p<0.05). On rotarod performance, latency-to-fall declined in mice administered citalopram, compared to control (p<0.05) at all time points, with no significant improvement after deprescribing. Preliminary history (n=3) suggests a non-significant trend towards increased myocardial fibrosis in High DBI mice. Our results indicate that chronic High DBI diet may impair therapeutic effects of cardiac drugs and increase cardiac collagen. Citalopram reduces endurance and it can be reversed with deprescribing. Future studies will continue to address histological changes involved.

**ELUCIDATING THE ROLE OF SMALL HEAT SHOCK PROTEIN 25 IN PROTEIN AGGREGATION**

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Both aging and many neurodegenerative disorders are characterized by protein aggregates, which may arise or be exacerbated by a failure of the protein homeostasis network. Small heat shock proteins (sHSP’s) are molecular chaperones that function not only in protein folding, but also improve the degradation activity of the proteasome and autolysosome, decreasing disease-associated aggregates. Previous work from our lab has shown that the expression level of small heat shock protein 25 (HSP25) in muscle and liver tissue correlates best with maximum lifespan potential in rodents, yet how this chaperone improves lifespan and the effect it may have on protein aggregation is unknown. To explore the role of HSP25 in longevity, we created a nematode overexpressing HSP25 from the naked-mole rat, and found that HSP25 improves lifespan potential and heat resistance in C. elegans. RNAi experiments suggest that the lifespan extension is dependent on hsf-1 and skn-1, but independent of daf-16. HSP25 overexpressing worms show an increase in cathepsin D activity, a marker of autophagy, and a decrease in trypsin-like cleavage, a marker of proteasome activity, though chymo-trypsin activity is elevated. HSP25 also has a beneficial effect on proteostasis in C. elegans models of neurodegeneration, including Huntington’s and Alzheimer’s disease models, as indicated by increases in lifespan and decreases heat-associated protein aggregation. These effects could reflect a shift in protein homeostasis from the use of the proteasome to the sequestration of toxic proteins by HSP25 followed by clearance via autophagy.

**ETHNIC-SPECIFIC EFFECT OF APOE ALLELES ON EXTREME LONGEVITY**

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Apolipoprotein E (APOE) is a well-studied gene with multiple effects on aging and longevity. The gene has 3 alleles: e2, e3 and e4 whose frequencies vary by ethnicity, and e4 is a known risk factor for Alzheimer’s, while e2 is associated with healthy aging and longevity. We analyzed ethnic specific effects of APOE alleles on extreme human longevity using genetic data of about 9,000 individuals from four studies of extreme longevity: the New England Centenarian Study, the Southern Italian Centenarian Study, the Longevity Gene Project, and the Long Life Family Study. The aggregated data comprised several European ethnicities and included 2144 cases of extreme longevity defined as individuals who lived past the 1 percentile survival age from the 1900 birth year cohort (i.e. age > 96 for males, and >100 years for females). For the analysis we used our new method PopCluster that combines logistic regression modeling, principal component analysis of genome-wide genetic data, hierarchical clustering, and a novel recursive bottom-up tree parsing procedure to automatically discover subsets of individuals in which the effects of a variant are statistically different. This analysis identified ethnically different clusters in which the effect of
APOE e2 and e4 alleles on extreme longevity changed substantially. For example, PopCluster discovered a group of Southern Italians with weaker protective effect of APOE e2 and weaker damaging effect of APOE e4 on extreme longevity compared to other European ethnicities. These results suggest possible interaction of this gene with nutrition habits or other environmental factors.

GENE CO-EXPRESSION NETWORKS FOR YOUNG AND OLD CD3+ SPLENOCYTES IN 3 MOUSE STRAINS
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Gene co-expression networks (GCNs) were derived for 130 immune-related genes obtained from CD3+ splenocytes extracted from FVB/N, C57BL/6N, and BALB/c mice at ages 2 and 24 months. Structure of the two different age-group networks was analyzed in order to understand potential age-related changes in network properties and their potential impact on understanding immunosenescence. Combining the three mouse lines by age, we found the GCN constructed for combined 2 month old mice was composed of 64 nodes and 85 edges, while the GCN for the combined 24 month old mice composed of 102 nodes and 302 edges. Power curve analysis demonstrated that the younger mouse GCN followed a power law behavior implying small world structure, while the older mouse group demonstrated a weak power law behavior. The small world network structure of the young CD3+ cells indicates that transcription of genes is tightly regulated within the splenocytes of 2 month old mice. Weak small world dynamics of the 24 month old mouse splenocytes suggests that this control is decreased/lost with age. This finding has implications for the regulatory behavior of genes in older T cells. Gene co-expression correlates with a number of biological processes, including cell signaling, protein complex formation, and transcription pathways. That the 24 month old mouse splenocytes see an increase in correlation at the expense of more robust network structures suggests T cell regulation and immune behavior is diminished. Consequently, this study suggests the need for further investigation into gene regulation in older T cells.

GENETIC INFLUENCE ON AGE OF MENOPAUSE IN THE LONG LIFE FAMILY STUDY AND HEALTH ANDRETIREMENT STUDY
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Several studies have observed that women who are able to naturally have children later in life tend to live longer. We hypothesize that the evolutionary pressure to extend the period of time in which women can bear children and therefore have the opportunity to have more of them could be a mechanism for the selection of genetic variants that slow aging and decrease risk for age-related diseases. While previous genetic studies have sought to discover genetic variants associated with age of menopause (AOM) in normally aging populations, our analysis aims to discover genetic variants that are associated with AOM in participants of the Long Life Family Study (LLFS), a cohort of families enriched for longevity, and combine the results with the Health and Retirement Study (HRS) in a meta-analysis. We meta-analyzed results from analysis of 1.5M single nucleotide polymorphisms (SNP) data of 4,457 women in the LLFS and HRS combined. We used Cox proportional hazard regression to model AOM accounting for censoring. We then sought replication using results from the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium 2015 meta-analysis of AOM. rs16999615 reached genome-wide significance and was previously found to be associated with an 11 month older AOM. There were also statistically suggestive novel SNPs on the X chromosome discovered in the LLFS data. Specifically, we found intronic variants of UTP14A, whose encoded proteins have anti-apoptotic roles in tumor cells.

HUMAN CIRCULATING MONOCYTES PHENOTYPES AND FUNCTIONS IN THE DEVELOPMENT OF ALZHEIMER’S DISEASE
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Alzheimer’s Disease is the most frequent neurocognitive disorder. The exact cause is not known however the neuroinflammation plays a key role. This neuroinflammation is more probably preceding the amyloid beta deposition in senile plaques. The innate immune system is playing a significant role in the neuroinflammation either in the brain (microglia) or in the periphery (monocytes). Our aim in the present work was to investigate the phenotypic and functional changes of monocytes in the progression of Alzheimer’s disease (AD). We evaluated four groups of subjects: healthy (HE), subjective memory complaint (SMC), amnestic Mild Cognitive Impairment (aMCI) and mildAD subjects (aged 60 to 85 years). We had 10 subjects per group. Monocytes were separated and studied by FACScan for their phenotypes and functions. Our results demonstrate that monocytes have a gradient of inflammatory phenotype (intermediate and non-classical) through the progression of the disease from HE to mAD subjects. The functions of monocytes are decreased through the progression of the disease. The differentiation of monocytes towards macrophages is skewed to the M1 phenotype. Our results demonstrate that monocytes may participate in the neuroinflammation as they cross the blood brain barrier and also as they become more and more inflammatory through the progression of the disease.

KYNURENIC ACID A TRYPHTHAN METABOLITE INDUCES BONE LOSS IN MICE
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