

GENETICS OF HEALTHY AGING: A POPULATION-BASED STUDY

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Living to the advanced age of eighty-five and beyond without developing age-related diseases is strived for by many but achieved by few. Fortunate individuals who achieve this goal may either lack susceptibility factors that contribute to age-related diseases in the majority of people, or may possess resistance factors that enhance their ability to resist disease and prolong lifespan. Healthy aging is considered to be a complex phenotype that is determined intrinsically by genes for which expression and physiological consequences are modified by extrinsic factors such as lifestyle and environment. Variation in such genes may contribute to a variety of processes that result in long-term good health.

A multidisciplinary team of researchers with expertise in genomics, genetics, gerontology, biostatistics, bioinformatics and cancer research has been formed to study healthy aging. Our objective is to identify "healthy aging" genes that contribute to exceptional health in old age. We will assess whether genetic variation including single nucleotide polymorphisms (SNPs) and haplotypes in these genes are associated with healthy aging by performing case/control based genetic association tests comparing exceptionally healthy seniors to ordinary middle-aged controls. The cases are healthy seniors over eighty-five chosen for freedom from cancer, cardiovascular disease, pulmonary disease, diabetes and Alzheimer disease who have a good quality of life.

Candidate genes are selected based on gene expression analysis (SAGE) of long-lived *C. elegans daf-2* mutants as well as from the literature. Exons and gene regulatory regions of candidate genes will be re-sequenced in forty-seven healthy seniors for discovery of novel genetic variations (SNPs, Insertions, and Deletions). A subset of variations will be chosen based on inter-marker linkage disequilibrium and putative functional relevance, and genotyped in 500 cases and 500 controls.