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Washington University-Led Team Wins Five-Year, $68M NIH Grant for Longevity Sequencing Study

Aug 23, 2019 | staff reporter

NEW YORK – An international team led by researchers at Washington University in St. Louis has been awarded $18.4 million from the National Institutes of Health for the first year of a five-year, approximately $68 million project to elucidate the genetic basis of exceptional human longevity.

Under the grant, being administered by the NIH's National Institute on Aging, the Long Life Family Study (LLFS) has enrolled 4,953 participants in 539 pedigrees in the US and Denmark that are enriched for exceptional longevity, and has measured them longitudinally in two extensive in-home visits "measuring key healthy aging phenotypes in all of the major domains of the aging process."

The researchers, led by principal investigator Michael Province of WUSTL, note that previous research has shown that "selecting on longevity in the first (proband) generation, results in the second (offspring) generation being much healthier than average in many key phenotypes. However, the pedigrees are heterogeneous by phenotype, with different families showing familial clustering of protection in cognition, grip strength, pulmonary function, blood pressure, et cetera."

In addition, they note, comprehensive linkage analysis of LLFS samples has identified "extremely strong genetic linkage peaks" for phenotypes for a wide variety of healthy aging features such as exceptional cognitive performance and lack of Alzheimer’s disease — peaks that are not explained by GWAS SNPs.

The researchers plan to conduct whole-genome sequencing on the LLFS cohort to identify the rare protective variants driving these linkage peaks. They also propose to continue longitudinal assessment of the cohort with additional in-person visits "to assess potential non-linear patterns of aging, and adding formal assessment of dementia diagnosis … which will increase specificity and power to discover and follow up on protective variants against Alzheimer's disease and other dementia diagnoses." The investigators also propose to phenotypically measure third-generation individuals to better resolve rare protective alleles.

The investigators said that they will conduct "extensive transcriptomics, methylomics, and proteomics" analyses on selected high-linkage pedigrees to begin to uncover protective gene variants and their modes of action. They will also perform metabolomics studies on the entire LLFS cohort to identify novel biomarkers of healthy aging and resistance to diseases such as Alzheimer's.

"Combined with a systems biology/network approach to data integration … such biomarkers would improve our power to detect even more novel protective genetic variants and identify the genetic signatures and pathways of genes conferring protection in this unique cohort to prevent onset of major

diseases such as diabetes, cardiovascular disease, cancer, and Alzheimer's disease and other dementia types," the researchers concluded.

According to WUSTL's Province, collaborators on the project include four field sites at Boston University, the University of Pittsburgh, Columbia University, and the University of Southern Denmark; a blood lab at the University of Minnesota; and additional analysis sites at the University of Maryland and Duke University.

WUSTL will serve as the data-coordinating, omics, and analysis center, Province said.

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