Unmasking Heterogeneity in Longitudinal Data: Biodemographic Genetic Analyses

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Background and Objective. Despite the fact, that many genetic variants associated with human aging and longevity traits are detected the mechanisms of these associations remain not well understood. In particular, it is unclear how these variants influence age patterns of physiological indices, incidence rates associated with major human diseases, cause-specific and all-cause mortality rates. The objective of this paper is to evaluate these associations.

Data and Methods. To address these problems we performed genome-wide association study of human lifespan using data collected in the original cohort of the Framingham Heart Study (FHS). The key feature of this approach is the proper use of information about age structure of study participants at the time of blood collection, their familial structure, right censoring and possible population stratification. Then we evaluated associations of detected genetic variants with risks of cancer of all sites but skin and with the risk of CVD. Using sets of detected genetic variants we constructed the "genetic dose" indices by counting the numbers of corresponding variants carrying by each study participant. Then we evaluated the influence of constructed indices on incidence, cause specific mortality, and all-cause mortality rates. We also evaluated effects of these indices on age trajectories of physiological indices including, blood glucose, diastolic blood pressure, systolic blood pressure, serum cholesterol, hematocrit, body mass index, and pulse rate.

Results. We found that a number of genetic variants associated with lifespan show pleiotropic associations: they are also significantly associated with age at onset of cancer and CVD. Some of these indices, however, show significant association only with cancer, and some others only with CVD. The analyses show substantial and highly significant associations of constructed polygenic score indices with risks of corresponding diseases. The analyses also show that study participants carrying different numbers of genes from selected sets have distinct age trajectories of physiological indices. We identified genes that are linked to detected genetic variants, investigated their functions, and their roles in metabolic pathways and disease networks using available Internet resources. Then we investigated how functions of detected genes can be linked with age patterns of observed aging related changes in phenotypic traits.

Conclusions. Genetic variants associated with lifespan are also associated with a number of other traits mediating genetic influence on lifespan. Studying connection of genetic functions with properties of age trajectories of physiological variables, age patterns of incidence, and cause specific mortality rates for groups of individuals with corresponding genetic backgrounds results in important insights and ideas about mechanisms of genetic regulation of longevity traits.